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[Intervention Review]

Oxygen therapy for acute myocardial infarction

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ABSTRACT

Background

Oxygen (O_2) is widely used in people with acute myocardial infarction (AMI). Previous systematic reviews concluded that there was insufficient evidence to know whether oxygen reduced, increased or had no effect on heart ischaemia or infarct size. Our first Cochrane review in 2010 also concluded there was insufficient evidence to know whether oxygen should be used. Since 2010, the lack of evidence to support this widely used intervention has attracted considerable attention, prompting further trials of oxygen therapy in myocardial infarction patients. It is thus important to update this Cochrane review.

Objectives

To assess the effects of routine use of inhaled oxygen for acute myocardial infarction (AMI).

Search methods

We searched the following bibliographic databases on 6 June 2015: the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (OVID), Embase (OVID), CINAHL (EBSCO) and Web of Science (Thomson Reuters). LILACS (Latin American and Caribbean Health Sciences Literature) was last searched in September 2016. We also contacted experts to identify eligible studies. We applied no language restrictions.

Selection criteria

Randomised controlled trials in people with suspected or proven AMI (ST-segment elevation myocardial infarction (STEMI) or non-STEMI) within 24 hours after onset, in which the intervention was inhaled oxygen (at normal pressure) compared to air, regardless of co-therapies provided to participants in both arms of the trial.

Data collection and analysis

Two authors independently reviewed the titles and abstracts of identified studies to see if they met the inclusion criteria and independently undertook the data extraction. We assessed the quality of studies and the risk of bias according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*. The primary outcome was death. The measure of effect used was the risk ratio (RR) with a 95% confidence interval (CI). We used the GRADE approach to evaluate the quality of the evidence and the GRADE profiler (GRADEpro) to import data from Review Manager 5 and create 'Summary of findings' tables.

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Main results

The updated search yielded one new trial, for a total of five included studies involving 1173 participants, 32 of whom died. The pooled risk ratio (RR) of all-cause mortality in the intention-to-treat analysis was 0.99 (95% CI 0.50 to 1.95; 4 studies, N = 1123; I^2 = 46%; quality of evidence: very low) and 1.02 (95% CI 0.52 to 1.98; 4 studies, N = 871; I^2 = 49%; quality of evidence: very low) when only analysing participants with confirmed AMI. One trial measured pain directly, and two others measured it by opiate usage. The trial showed no effect, with a pooled RR of 0.97 for the use of opiates (95% CI 0.78 to 1.20; 2 studies, N = 250). The result on mortality and pain are inconclusive. There is no clear effect for oxygen on infarct size (the evidence is inconsistent and low quality).

Authors' conclusions

There is no evidence from randomised controlled trials to support the routine use of inhaled oxygen in people with AMI, and we cannot rule out a harmful effect. Given the uncertainty surrounding the effect of oxygen therapy on all-cause mortality and on other outcomes critical for clinical decision, well-conducted, high quality randomised controlled trials are urgently required to inform guidelines in order to give definitive recommendations about the routine use of oxygen in AMI.

PLAIN LANGUAGE SUMMARY

Routine use of oxygen in people who have had a heart attack

Background

Many people who are having a heart attack are routinely given oxygen to breathe.

Review question

We looked for the evidence to support this longstanding practice by searching for randomised controlled trials that compared the outcomes for people given oxygen versus normal air to breathe. We were primarily interested in seeing whether there was a difference in the number of people who died, but we also looked at whether administering oxygen reduced pain or other adverse outcomes.

Key results

We found five randomised controlled trials that compared people with suspected or proven heart attack who were given oxygen to a similar group of people who were given air (evidence is current to June 2016). These trials involved a total of 1173 participants, 32 of whom died. There were similar death rates in both groups, suggesting oxygen neither helps nor harms, but the trials are not big enough to know for sure. Moreover, it is possible that more heart muscle might be damaged in people given oxygen than in people given air.

Conclusion

Since there is no evidence whether the oxygen is good or harmful in this clinical condition, it is important to test oxygen in a big trial as soon as possible to be sure that this common treatment is doing more good than harm in people who are having a heart attack.

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Summary of findings for the main comparison. Oxygen versus air for acute myocardial infarction

Oxygen versus air for acute myocardial infarction

Patient or population: people with acute myocardial infarction
Settings: pre-hospital and hospital
Intervention: oxygen

Comparison: air

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Air (or titrated oxygen)	Oxygen				
All-cause mortality in hospital for participants with AMI Follow-up: 4 weeks	**Study population**		**RR 1.02** (0.52 to 1.98)	871 (4 studies)	⊕⊝⊝⊝ **Very low** [a]	—
	36 per 1000	**37 per 1000** (19 to 71)				
	Moderate population					
	34 per 1000	**35 per 1000** (18 to 67)				
All-cause mortality in hospital for all participants (including those without confirmed AMI) Follow-up: 4 weeks	**Study population**		**RR 0.99** (0.50 to 1.95)	1123 (4 studies)	⊕⊝⊝⊝ **Very low** [b]	—
	28 per 1000	**28 per 1000** (14 to 55)				
	Moderate population					
	29 per 1000	**29 per 1000** (15 to 57)				
All-cause mortality in hospital for all participants (including those without confirmed AMI) trials done in the revascularisation era Follow-up: 4 weeks	**Study population population**		**RR 0.58** (0.24 to 1.39)	923 (3 studies)	⊕⊕⊝⊝ **Low** [c]	—
	27 per 1000	**16 per 1000** (7 to 38)				

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	Moderate population					
	26 per 1000	**15 per 1000** (6 to 36)				
Opiate use (as a proxy measure for pain) for all participants on ITT (including those without confirmed AMI) Follow-up: 4 weeks	**Study population**		**RR 0.97** (0.78 to 1.20)	250 (2 studies)	⊕⊕⊖⊖ **Low** [d]	
	583 per 1000	**566 per 1000** (455 to 700)				
	Moderate population					
	634 per 1000	**615 per 1000** (495 to 761)				
Recurrent myocardial infarction (or ischaemia) Follow-up 4 weeks	**Study population**		**RR 1.67** (0.94 to 2.99)	578 (2 studies)	⊕⊕⊕⊖ **Low** [e]	—
	64 per 1000	**87 per 1000** (50 to 152)				
	Moderate population					
	140 per 1000	**190 per 1000** (109 to 333)				
Infarct size CK and other enzymes	See comment	See comment	Not estimable	0 (2 studies)	⊕⊖⊖⊖ **Low**	The are slight inconsistencies between 2 trials with respect to the effect of oxygen on CK levels (Ukholkina 2005 and Stub 2015). There are inconsistency in the effect of oxygen on CK levels and the effect on troponin I in Stub 2015 (whitin study inconsistency).
Infarct size by MRI (estimated 6 months after AMI)	See comment	See comment	Not estimable	0 (2 studies)	⊕⊖⊖⊖ **Very low**	The evidence for this outcome comes from 2 randomised trials but in 'selected' groups of patients,. As the data comes from with non-randomised comparisons and was performed 6 months after AMI, we con-

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sidered them unsuitable for quantitative synthesis.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMI: acute myocardial infarction; **CI**: confidence interval; **MRI**: magnetic resonance imaging; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]The evidence for this outcome has very serious limitations due to incomplete outcomes data in 2 of the 4 included studies (Ranchord 2012; Ukholkina 2005); downgraded 2 levels. An additional level is applied for imprecision.
[b]Downgraded 2 levels for very serious limitations due to incomplete data outcomes in 2 of 4 studies (Ranchord 2012; Ukholkina 2005). An additional point deducted for imprecision.
[c]The evidence for this outcome has serious limitations due to incomplete data in 2 of the 3 studies (Ranchord 2012; Ukholkina 2005), but the other one study with low risk of bias is the most weighted in meta analysis (82.3%) (Stub 2015), so the quality is downgraded 1 level. An additional point deducted for imprecision.
[d]The evidence for pain comes from a blinded study with unclear risk of bias and another unblinded study with high risk of bias for a subjective outcome; downgraded one level. An additional point deducted for indirectness (opiate is used as proxy for pain).
[e]Downgraded for imprecision and for inconsistency

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BACKGROUND

Description of the condition

Coronary heart disease (CHD) is an important cause of death worldwide. Over 7 million people every year die from CHD, accounting for 12.8% of all deaths (WHO 2011). It is the single most common cause of death before the age of 75 in Europe (Townsend 2015), and in the USA it accounted for around one of every seven deaths in 2011 (Mozaffarian 2015), although deaths from cardiovascular disease and CHD in men and women have fallen in most developed countries. For example, rates of CHD deaths per million in men without diabetes in England fell by more than half between 1995 and 2010 (Ecclestone 2015). According to the Euro Heart Survey of acute myocardial infarction (AMI) in 47 countries (Puymirat 2013), in-hospital mortality was 6.2%. Approximately 45% of the reduction in CHD mortality is attributable to improvement in medical therapies for coronary disease (Capewell 2000).

A common manifestation of CHD, often the first, is AMI. The third Global MI Task Force defines AMI as "any evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia" (Thygesen 2012).

Myocardial ischaemia is usually the result of spontaneous complications of atherosclerosis (plaque rupture, ulceration, fissuring, erosion or dissection) resulting in coronary thrombosis (type 1 AMI). Other categories of AMI include: those produced by underlying CHD with an ischaemic imbalance attributable to a wide range of factors including endothelial dysfunction, coronary spasm, coronary embolism, tachy-/brady-arrhythmias and hypo- and hypertension (type 2 AMI); sudden cardiac death induced by myocardial ischaemia (type 3 AMI); and AMI occurring in the context of invasive coronary procedures such as percutaneous coronary intervention (PCI), in-stent thrombosis, or coronary artery bypass grafting (CABG), categorised as subtypes 4a, 4b and 5 of AMI. By far the most common types of AMI are types 1 and 2, to such an extent that their incidence may be used as proxy variables to estimate the prevalence of CHD in the general population. Hereafter we will use the term 'AMI' to refer the type 1 and type 2 AMI.

Myocardial injury may be detected through: highly sensitive biochemical markers such as troponin (I or T), or the MB fraction of the creatine kinase (CK-MB); electrocardiographic changes; or imaging techniques such as echocardiography, magnetic resonance imaging (MRI) or radionuclide imaging. Necessary criteria to diagnose AMI in a clinical context include a change (rise and/or fall) in cardiac biomarker values, together with at least one of the following: ischaemic symptoms, typical electrocardiographic changes, or abnormalities in the structure or wall motion of the heart identified by imaging techniques.

Moreover, the recognition that acute coronary syndromes represent a spectrum of pathophysiological processes rather than a uniform type of 'heart attack' has led to publication of separate guidelines with different therapeutic options for AMI presenting with persistent ST-segment elevation (STEMI) and non-STEMI (NSTEMI) presentations.

The in-hospital mortality rate of unselected STEMI patients according to the Euro Heart Survey, published by the European Society of Cardiology, varies between 6% and 14% (Mandelzweig 2006). The most serious complications of AMI are cardiogenic shock, heart failure, ventricular fibrillation and recurrent ischaemia. Around 8% of people with AMI develop cardiogenic shock (Babaev 2005), but this remains present in 29% of those people on admission to hospital. The Global Registry of Acute Coronary Events (GRACE) reported that heart failure occurred in 15.6% of people with STEMI and 15.7% of those with NSTEMI, but heart failure was present in only 13% of these patients on admission to hospital (Steg 2004). Ventricular fibrillation occurred in 1.9% of people with AMI (Goldberg 2008), and 21% of those with acute coronary syndromes presented with recurrent ischaemia (Yan 2010), about half of whom experienced this outcome in the first 24 hours. Other possible complications of AMI include pericarditis, mitral insufficiency, arrhythmias and conduction disturbances.

The cornerstone of contemporary management of people with STEMI is reperfusion therapy, with either primary percutaneous coronary intervention (PCI) or thrombolytic treatment if less than 12 hours has elapsed from the onset of symptoms. Other recommended treatments in international guidelines include morphine, oxygen (O_2), nitrates and aspirin (MONA) (O'Connor 2010; O'Gara 2013; Steg G 2012). Some of these treatments have a well-established research base, while others do not (Nikolaou 2012; O'Driscoll 2008; SIGN 2010).

Description of the intervention

Inhaled oxygen at normal pressure delivered by face mask or nasal cannula, at any concentration.

How the intervention might work

Myocardial infarction occurs when the flow of oxygenated blood in the heart is interrupted for a sustained period of time. The rationale for providing supplemental oxygen to a person with AMI is that it may improve the oxygenation of the ischaemic myocardial tissue and reduce ischaemic symptoms (pain), infarct size and consequent morbidity and mortality.

Why it is important to do this review

Although it is biologically plausible that oxygen is helpful, it is also biologically plausible that it may be harmful. Potentially harmful mechanisms include the paradoxical effect of oxygen in reducing coronary artery blood flow and increasing coronary vascular resistance, measured by intracoronary Doppler ultrasonography (McNulty 2005; McNulty 2007); reduced stroke volume and cardiac output (Milone 1999); other adverse haemodynamic consequences, such as increased vascular resistance from hyperoxia; and reperfusion injury from increased oxygen free radicals (Rousseau 2005), which may also have adverse electrophysiological effects, triggering lethal arrhythmias (Xie 2009).

A systematic review of human studies that included non-randomised studies did not confirm that oxygen administration diminishes acute myocardial ischaemia (Nicholson 2004). Indeed, some evidence suggested that oxygen may increase myocardial ischaemia (Nicholson 2004). Another narrative review of oxygen therapy also sounded a cautionary note (Beasley 2007). It referenced a randomised controlled trial (RCT) conducted in 1976 showing that the risk ratio (RR) of death was 2.89 (95% confidence interval (CI) 0.81 to 10.27) in participants receiving oxygen compared to those breathing air (Rawles 1976). While this suggested that oxygen may be harmful, the increased risk of death

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could easily have been a chance finding. A systematic review looked at the effect of oxygen on infarct size in people with AMI and concluded that "[t]here is little evidence by which to determine the efficacy and safety of high flow oxygen therapy in MI. The evidence that does exist suggests that the routine use of high flow oxygen in uncomplicated AMI may result in a greater infarct size and possibly increase the risk of mortality" (Wijesinghe 2009).

Despite this lack of robust evidence of effectiveness prior to the publication of our 2010 Cochrane review of the evidence, international guidelines widely recommended oxygen administration (AARC 2002; AHA 2005; Anderson 2007; Antman 2002; ILCOR 2005; Van de Werf 2008). Some guidelines were more cautious; for example, the European guideline did not recommend routine oxygen use in acute coronary syndrome (ACS) (Bassand 2007), and the Scottish Intercollegiate Guidelines Network (SIGN) guidance only recommended oxygen use in hypoxaemia (< 90% saturation), noting that there was no clinical evidence for its effectiveness and referring to animal models that showed a reduction in infarct size (SIGN 2007).

Guidelines published since the 2010 Cochrane review have tended to move to a more cautious position reflecting the lack of evidence. In 2010, for example, the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular care stated that: "EMS providers administer oxygen during the initial assessment of patients with suspected ACS. However, there is insufficient evidence to support its routine use in uncomplicated ACS. If the patient is dyspnoeic, hypoxaemic, or has obvious signs of heart failure, providers should titrate therapy, based on monitoring of oxyhaemoglobin saturation, to 94% (class I, level of evidence: C). Updated SIGN guidance states, "A Cochrane review found no conclusive evidence from randomised controlled trials to support the routine use of inhaled oxygen in patients with AMI. There is no evidence that routine administration of oxygen to all patients with the broad spectrum of acute coronary syndromes improves clinical outcome or reduces infarction size" (SIGN 2010).

In 2011 an addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS), authors stated that "There is currently insufficient evidence to formulate clear recommendations about oxygen therapy . . . Definitive trials are needed to answer this question" (Chew 2011).

Similarly, the 2012 ESC guidelines for STEMI, citing the Cochrane review, now state: "Oxygen (by mask or nasal prongs) should be administered to those who are breathless, hypoxic, or who have heart failure. Whether oxygen should be systematically administered to patients without heart failure or dyspnoea is at best uncertain. Noninvasive monitoring of blood oxygen saturation greatly helps when deciding on the need to administer oxygen or ventilator support" (Steg G 2012).

The 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction shows a similar change in emphasis: "Few data exist to support or refute the value of the routine use of oxygen in the acute phase of STEMI, and more research is needed. A pooled Cochrane analysis of 3 trials showed a 3-fold higher risk of death for patients with confirmed AMI treated with oxygen than for patients with AMI managed on room air. Oxygen therapy is appropriate for patients who are hypoxaemic (oxygen saturation < 90%) and may have a salutary placebo effect in others. Supplementary oxygen may, however, increase coronary vascular resistance. Oxygen should be administered with caution to patients with chronic obstructive pulmonary disease and carbon dioxide retention". (O'Gara 2013).

The British Heart Foundation (BHF), in response to the doubts about oxygen use raised by Beasley 2007, originally stated in an article in *The Guardian* in 2007 that "[t]he current practice of giving high-flow oxygen is an important part of heart attack treatment. Best practice methods have been developed and refined over the years to ensure the best possible outcome for patients. There is not enough evidence to change the current use of oxygen therapy in heart attacks". Five years after the publication of the first Cochrane Review, the use of oxygen in AMI and across the spectrum of coronary acute syndromes is still controversial (Shuvy 2013). We think that, given the evidence cited, it would have been more appropriate to conclude that despite decades of use there is inadequate clinical trial evidence to unequivocally support routine administration of oxygen. The BHF subsequently stated that the 2010 Cochrane review "highlights the need for more research into the effects of oxygen when it is given during a heart attack. Until recently, heart attack patients were routinely treated with oxygen but we simply do not have enough evidence to know if that treatment is beneficial or harmful" (BHF 2010).

Despite the attention given to the uncertainty around the role of oxygen since our 2010 Cochrane review, practice appears to vary, possibly because the evidence base informing current guideline recommendations remains uncertain. A survey of 231 cardiac care units in the UK undertaken shortly after the 2010 review reported that only a third adhered to guideline recommendations to titrate oxygen to saturation rather than administer routinely, and practice was no different in hospitals that had formal oxygen therapy policies versus those that did not (Ripley 2012).

With the lack of collective certainty about the use of oxygen, a number of clinical trials are now underway or have recently been reported to reassess this treatment. In general, practice should not be based on tradition but on proven benefit and safety. Given that the 1976 trial was suggestive of potential harm from oxygen in suspected AMI (Rawles 1976), it is important to systematically review and update the evidence base for current and future guidance regarding the role of oxygen therapy in heart attack patients, and if necessary, to undertake further research to clarify whether this intervention does more harm than good. If the only robust evidence is suggestive of potentially serious harm, even if the result is not statistically significant, it reinforces our opinion that this intervention should not be routinely used, however sound the pathophysiological reasoning.

OBJECTIVES

To assess the effects of routine use of inhaled oxygen for acute myocardial infarction (AMI). Primary outcomes include death and pain.

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METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of parallel or cluster design, in any language, with any length of follow-up, and with any publication status (full publication, abstract only or unpublished).

Types of participants

Adults of any age treated, in a pre-hospital or a hospital setting, for suspected or proven AMI (STEMI or NSTEMI), within 24 hours of symptoms onset, regardless of any co-therapy (for example a reperfusion therapy) provided to both arms of the trial.

Types of interventions

The intervention is routinely given inhaled oxygen administered by any device at normal pressure for one hour or more within 24 hours of AMI symptoms onset. The comparator is air, or air with titrated oxygen in the event of desaturation.

Excluded interventions are hyperbaric oxygen or aqueous oxygen therapy (unless the studies include arms with air or oxygen at normal pressure).

Types of outcome measures

This review is primarily focused on clinically important outcomes. To facilitate the assessment of the clinical importance of outcomes we used the nine-point scale suggested by GRADE (Guyatt 2008), which classifies the outcomes into three levels of importance. The outcomes included in the review are type I ("critical for decision-making"- ratings 9, 8, 7) and also type 2 ("important but not critical for decision-making"- ratings 6, 5, 4). We did not include the type 3 outcomes: ("not important for decision-making, of lower importance to patients" - ratings 3, 2, 1). We pre-specified mortality as the primary outcome. We agreed the point on the GRADE scale for each outcome through discussion within the review team, where we easily reached a consensus. We showed our proposed classifications to cardiologist colleagues to see whether they agreed with them. Although there were one-point differences in some of their assessments of the importance of particular outcomes, none of these affected the level of importance into which we classified an outcome.

We classified the following outcomes as type I (the review group's consensus score is given in brackets).

- All-cause mortality (9).
- Cardiac mortality (9).
- Cardiac failure (8).
- Stroke (8).
- Recurrence of myocardial infarction or ischaemia (8).
- Major bleeding (8).
- Pain (7).
- Revascularisation (7).
- Pericarditis (7).
- Arrhthymias (7).

We classified the following outcomes as type 2 outcomes.

- Left ventricular function (global and segmentary) (6).
- Infarct size, whether estimated using biological methods (electrocardiogram (ECG), enzymes CK, CK-MB, troponin T or troponin I, brain natriuretic peptide (BNP)) or imaging techniques such as magnetic resonance imaging (MRI), or echocardiography (5).

We classified the following outcomes as type 3 outcomes.

- ECG changes (4).
- Platelet aggregation (3).
- Biomarkers of oxidative stress (2).
- Apoptosis (2).
- Inflammation (2).

Although these outcomes may prove useful for helping understand the disease process, they currently have little implication for decision-making or prognosis.

We used standard direct measures for all types of outcomes. For the case of pain, when the direct measurement was not available we used the opiate dosage as a proxy for pain. This approach (response to treatment) is classically used when validating pain scales. We have included type 2 outcomes because they may be used to make clinical decisions or recommendations.

Search methods for identification of studies

Electronic searches

We searched the following bibliographic databases (from inception to 6 June 2016).

- Cochrane Central Register of Controlled Trials (CENTRAL, 2016, Issue 5) in the Cochrane Library.
- MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE Ovid (1946 to 6 June 2016).
- Embase Ovid (1980 to 2016 week 23).
- PubMed (2012 to 4 June 2015).
- CINAHL Plus (EBSCO, 1937 to 6 June 2016).
- Web of Science Core Collection (Thomson Reuters, 1970 to 6 June 2016).

We also searched LILACS (Latin American and Caribbean Health Sciences Literature) in BIREME (Centro Latinoamericano y del Caribe de Información en Ciencias de la Salud) from 2012 to 22 September 2016. (lilacs.bvsalud.org).

We applied the sensitivity-maximising version of the Cochrane RCT search filter to the MEDLINE searches and its adaptations to Embase, CINAHL Plus and Web of Science (Lefebvre 2011).

We searched the following databases for ongoing trials using the search terms "(Acute myocardial infarction AND oxygen as search strategy)" (12 September 2016).

- Current Controlled Trials metaRegister (www.controlled-trials.com/mrct).
- The European Union Clinical Trials Register (www.clinicaltrialsregister.eu/about.html).
- International Clinical Trials Registry Platform (ICTRP), World Health Organization (www.who.int/ictrp/network/en/)

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Details of the database search strategies are in Appendix 1 (for 2010), Appendix 2 (for 2012), Appendix 3 (for 2015) and Appendix 4 (for 2016).

Searching other resources

We searched proceedings of annual meetings and conferences of professional bodies (American Heart Association, British Cardiovascular Society, European Society of Cardiology and American College of Cardiology) for relevant abstracts (from August 2013 to 4 June 2015).

We contacted experts in the field to locate any unpublished studies and checked citations from key references.

We applied no date or language restrictions to the searches.

Data collection and analysis

We used the standard methods of Cochrane as described in the *Cochrane Handbook for Systematic Reviews of Interventions* so that the review methods are consistent with current recommendations (Higgins 2011). We used Review Manager 5 (RevMan 5) for the analysis (RevMan 2014).

Selection of studies

Two authors independently reviewed the titles and abstracts of studies identified in the searches to see if they met the above inclusion criteria. We obtained study reports in full text when inclusion could not be decided from the title or abstract.

Data extraction and management

Two authors independently evaluated the methodological quality and undertook independent data extraction using an agreed data extraction form. We resolved differences by discussion. One review author entered the data into RevMan 2014, and two others checked them.

Assessment of risk of bias in included studies

Risk of bias in individual studies

We used the two-part tool described in section 8.5 of Higgins 2011. We explored the six specific domains: sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting, and other potential threats to validity.

For each trial, two review authors first independently described the design characteristics relating to each domain and then judged the risk of bias associated with the main outcome. We used a nominal scale for the judgement: low, high or unclear risk of bias.

Risk of bias across studies

We did an overall assessment of risk of bias for every outcome within the review for each domain, using a similar scale: low risk of bias in all domains, unclear risk of bias for one or more domains, and high risk of bias for one or more domains.

When we undertook meta-analysis, we summarised the risk of bias for the main outcomes across studies. We resolved disagreements between review authors in the description or in the judgement by consensus, without the need for recourse to a third review author.

Measures of treatment effect

We looked at the risk ratio (RR) of death and reported this rather than the risk difference. We also looked for differences in mean pain scores; if studies did not report these scores, we used the RR of opiate use as a proxy measure for pain intensity. We used the differences in mean for continuous measurement of infarct size such as cardiac enzymes, troponin T, BNP or MRI.

Unit of analysis issues

The earliest trial randomised 200 participants, but authors only analysed the results for the 157 who were later confirmed to have had an AMI (Rawles 1976). Ranchord 2012 also excluded five participants in whom AMI was not confirmed and seven withdrawn participants from the analysis. In the newly included trial involving 638 participants with suspected AMI, randomised by paramedic personnel in the ambulance, investigators excluded 50 for different reasons and assessed 588 for STEMI upon hospital arrival (Stub 2015). Angiography was indicated (and performed) in 470 participants with clinical diagnosis of AMI. Physicians ruled out STEMI in 29 participants (17 in the oxygen group and 12 in the air) and confirmed it in only 441 patients, in whom investigators measured the primary outcome (infarct size estimated by troponin peak cTnI and CK). The other patients were excluded from the primary analysis, but many clinical data including mortality are available.

It is legitimately open for debate whether people who did not have an AMI should be included in a study of the benefits of oxygen in AMI. Theoretically, diagnosis may be more certain today, but not at symptoms onset, and of course a hospital physician will be able to more accurately diagnose AMI than paramedics in the ambulance. On the other hand, we treat suspected MIs, and these represent some of the people to whom a treatment would be given in practice.

We have therefore performed two analyses: one in participants who had confirmed AMI in Rawles 1976, Ukholkina 2005, Ranchord 2012 and Stub 2015, and a second that also covered all participants from the trials in a strict intention-to-treat (ITT) analysis that included the 43 participants from Rawles 1976 who did not have an AMI confirmed, the 12 withdrawn participants from Ranchord 2012, and the 197 (of the 638 randomised participants) from Stub 2015 in which STEMI was ruled out. This was to preserve the strict randomisation process and to minimise selection bias.

Dealing with missing data

We contacted study authors for missing data.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the outcomes tables of the different analysis and using the I^2 statistic (where I^2 > 50% was considered substantial or considerable heterogeneity) (Higgins 2003).

Assessment of reporting biases

As there were only five studies that met the inclusion criteria, it was not possible to explore reporting bias using funnel plots or the Begg and Egger tests (Begg 1994; Egger 1997).

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Data synthesis

We undertook meta-analyses where data were available and it was clinically sensible to do so, using both fixed-effect and random-effects models. We reported the results using both models because we recognise that readers may have different perspectives (for example preconceptions, values or contexts) and different people may wish to see the results with the different mathematical assumptions.

Subgroup analysis and investigation of heterogeneity

The data were too sparse to permit adequate exploration of all the subgroups that had been pre-specified for analysis (such as timing and duration of oxygen therapy, pre-existing levels of hypoxaemia or other measures of severity of infarction). We undertook an analysis including only the trials undertaken during the reperfusion era, as these reflect today's clinical practice. We define 'reperfusion era' as the period in which thrombolysis, PCI or CABG were generalised as the main treatment for AMI (since 1985).

Sensitivity analysis

Similarly, our intention to explore the effect of trial quality in a sensitivity analysis was limited by the number of trials and the quality of reporting. We undertook separate analyses using the confirmed AMI population and the ITT population, and undertook 'best-case' and 'worst-case' scenarios in sensitivity analysis for the missing data on deaths (Wilson 1997).

Summary of findings table

We created a 'Summary of findings' table for the outcomes all-cause mortality in hospital for participants with AMI, all-cause mortality in hospital for all participants, all-cause mortality in hospital for all participants in trials done in the revascularisation era, opiate use as a proxy measure for pain, recurrent myocardial infarction, infarct size by CK and other enzymes, and infarct size by MRI. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Guyatt 2008). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro software (GRADEpro; Higgins 2011). We justified all decisions to down- or upgrade the quality of studies using footnotes, and we made comments to aid readers' understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

We identified 204 new records with the updated search in June 2016. The removal of duplicates left 136 new records for screening. Based on title and abstract, we excluded 111 papers and retrieved 25. Ten were reviews, editorials or non-randomised studies, three RCTs were not relevant to our purpose, and five were references for ongoing trials. The remaining seven records all reported one new randomised controlled trial that was eligible for inclusion (Stub 2015): three were conference abstracts, one was the protocol, one was the main study, and the remaining two were respectively a subgroup study and re-analysis of the same study. We describe the process in Figure 1.

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Figure 1. Study flow diagram with previous included studies incorporated into the results of the updated literature search.

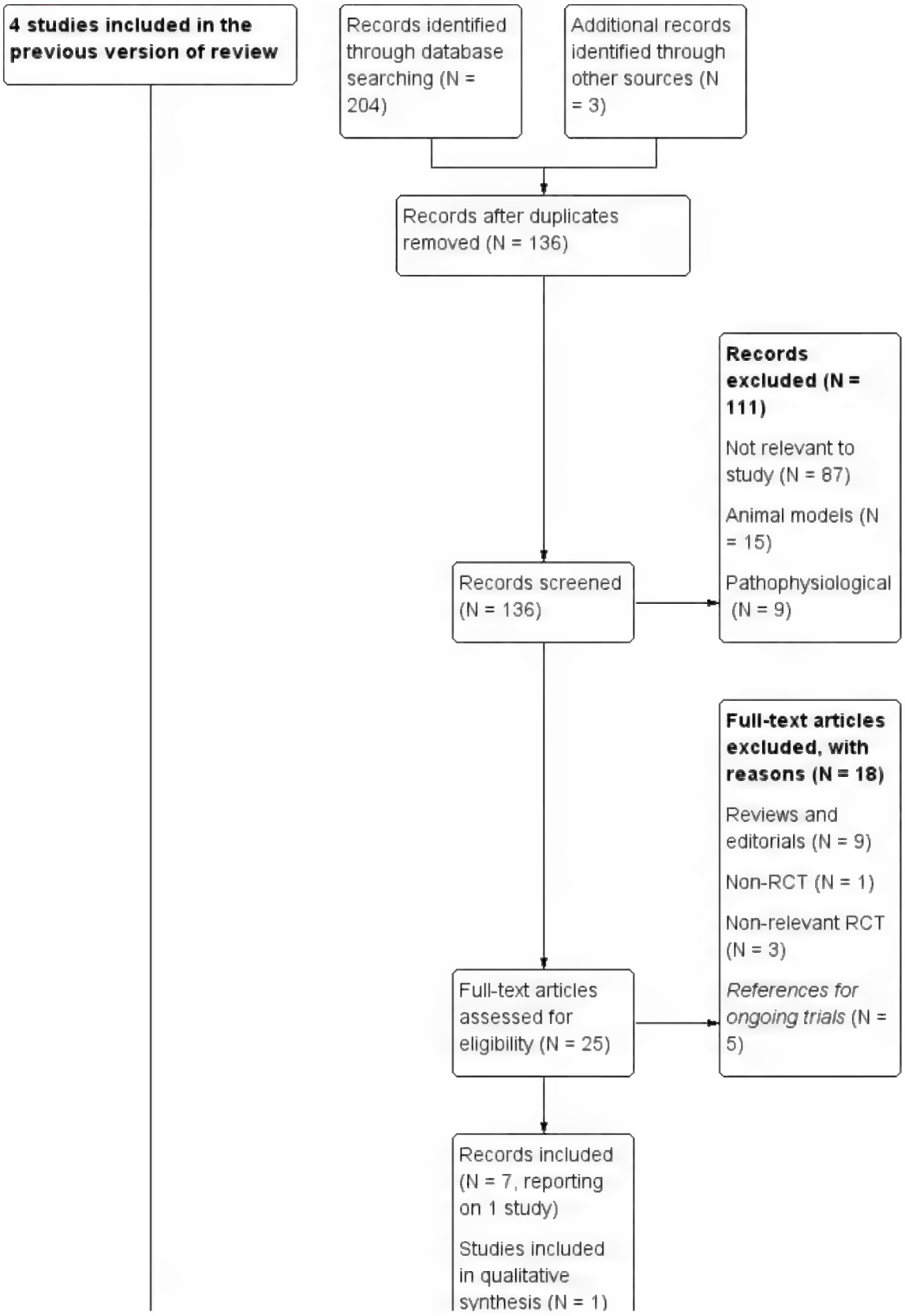
4 studies included in the previous version of review
Records identified through database searching (N = 204)
Additional records identified through other sources (N = 3)
Records after duplicates removed (N = 136)
Records excluded (N = 111)
Not relevant to study (N = 87)
Animal models (N = 15)
Pathophysiological (N = 9)
Records screened (N = 136)
Full-text articles excluded, with reasons (N = 18)
Reviews and editorials (N = 9)
Non-RCT (N = 1)
Non-relevant RCT (N = 3)
References for ongoing trials (N = 5)
Full-text articles assessed for eligibility (N = 25)
Records included (N = 7, reporting on 1 study)
Studies included in qualitative synthesis (N = 1)

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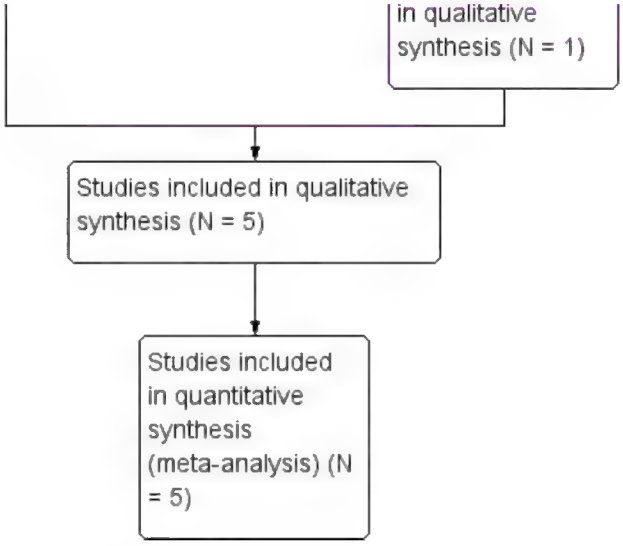
Figure 1. (Continued)


in qualitative synthesis (N = 1)
Studies included in qualitative synthesis (N = 5)
Studies included in quantitative synthesis (meta-analysis) (N = 5)

Including the papers identified in the previous version of the review, we retrieved a total of 2892 records and screened 2442 unique records (Figure 2). Based on title and abstract, we excluded 2268 and retrieved 174 full papers retrieved. We excluded a further 162 articles, as 138 were not RCTs or were RCTs not related to our review, 16 were excluded for various other reasons, 5 were references for ongoing studies (NCT01787110; NCT02290080), and 3 were ongoing trials identified in the previous version of this review (old ongoing trials). This left 12 papers reporting five trials that met the inclusion criteria (Ranchord 2012; Rawles 1976; Stub 2015; Ukholkina 2005; Wilson 1997). We describe the process with reasons for exclusion in Figure 2 and the list of excluded trials in Characteristics of excluded studies.

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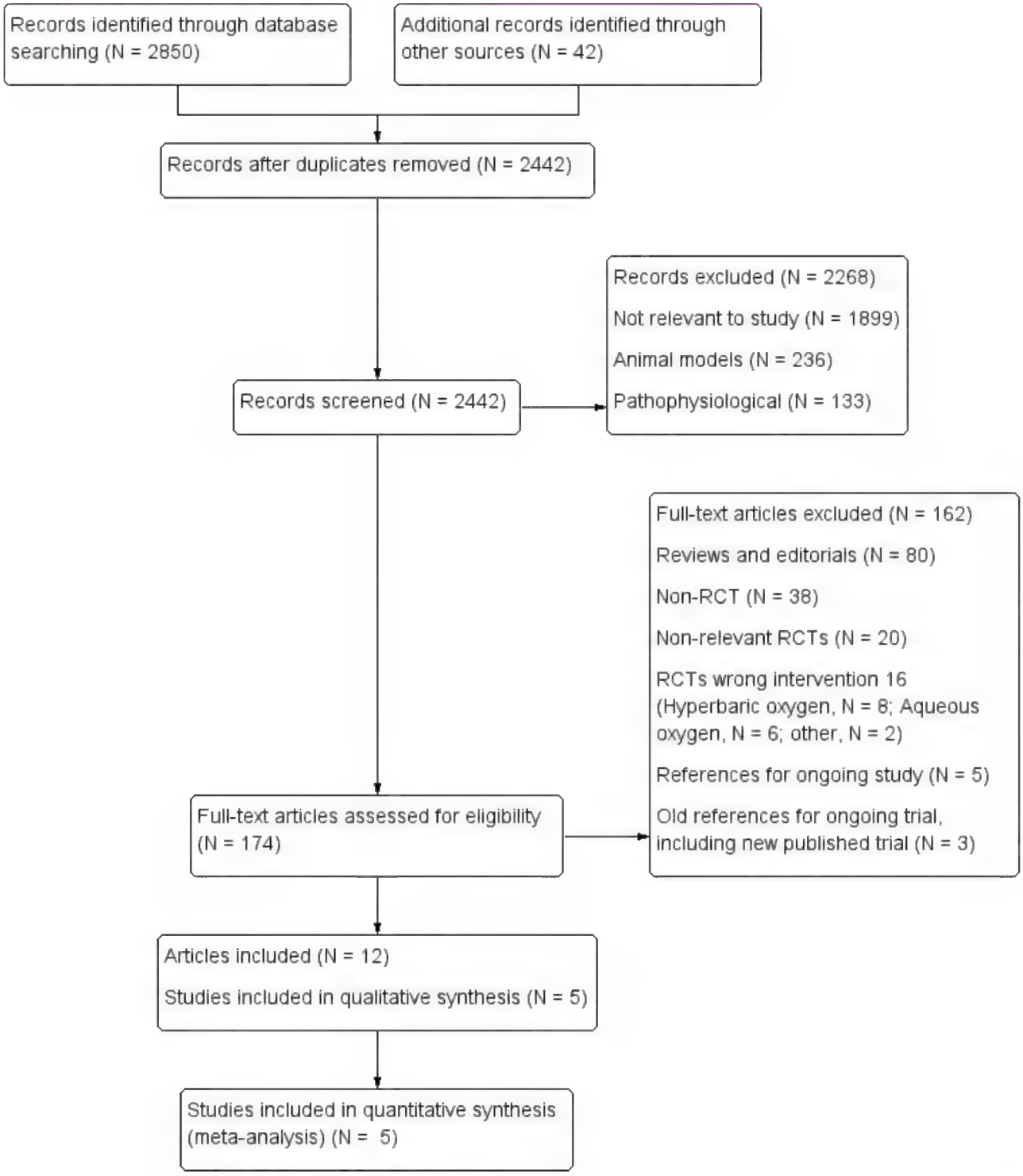
Figure 2. Study flow diagram (cumulative searches)


Records identified through database searching (N = 2850)
Additional records identified through other sources (N = 42)
Records after duplicates removed (N = 2442)
Records excluded (N = 2268)
Not relevant to study (N = 1899)
Animal models (N = 236)
Pathophysiological (N = 133)
Records screened (N = 2442)
Full-text articles excluded (N = 162)
Reviews and editorials (N = 80)
Non-RCT (N = 38)
Non-relevant RCTs (N = 20)
RCTs wrong intervention 16 (Hyperbaric oxygen, N = 8; Aqueous oxygen, N = 6; other, N = 2)
References for ongoing study (N = 5)
Old references for ongoing trial, including new published trial (N = 3)
Full-text articles assessed for eligibility (N = 174)
Articles included (N = 12)
Studies included in qualitative synthesis (N = 5)
Studies included in quantitative synthesis (meta-analysis) (N = 5)

With respect to the three ongoing trials identified in the previous version of this review, we included one of them in this review (Stub 2015). The protocol of a second study has been published as paper but the final report has not (NCT01423929). The third protocol, identified exclusively by trials register, has not started, and the register had reported no activity as of September 2016 (ACTRN12609000466246). We therefore maintained these two last trials as ongoing trials in this version of the review.

In total, we identified four ongoing trials as of September 2016 (see Characteristics of ongoing studies). All four are parallel designs to compare oxygen (O_2) versus air in people with suspected acute myocardial infarction (AMI). In the first study, the main outcome is in-hospital mortality (this study, despite having been registered in 2009, has not yet commenced recruitment (ACTRN12609000466246). In the second study, the primary outcome is infarct size estimated by magnetic resonance

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imaging (MRI) and myocardial salvage index by MRI (NCT01423929); in the third study, the main outcome is one year all-cause mortality, while secondary outcomes are 30-days mortality as well as major adverse cardiac events (MACE) at 30 days and one year, including reinfarction and hospitalisations for cardiac failure (NCT01787110). This third study has nested a fourth trial with a slightly different architecture and oriented exclusively to biochemical outcomes (NCT02290080).

Included studies

The five included trials took place between 1976 and 2015 (Ranchord 2012; Rawles 1976; Stub 2015; Ukholkina 2005; Wilson 1997). Two were conducted in the UK (Rawles 1976; Wilson 1997), one in Russia (Ukholkina 2005), one in New Zealand (Ranchord 2012), and one in Australia (Stub 2015). All five studies were parallel-design, randomised controlled trials. Rawles 1976 was double-blind, and the other four were open-label.

Population: a total of 1173 participants were involved, of whom 75.3% were men. Three studies recruited participants with suspected AMI (Ranchord 2012; Rawles 1976; Stub 2015), and the other two included only people with confirmed AMI (Ukholkina 2005; Wilson 1997). The mean ages in years (and standard errors where given) of the included participants in each group were as follows: Rawles 1976: air, 50.8 years (SE 2.4); O_2, 51.3 years (SE 1.7); Wilson 1997: air, 64 years; O_2, 65 years; Ukholkina 2005: air, 53.5 years (SE 1.06); O_2, 55.6 years (SE 1.33); Ranchord 2012: air, 60 years (SE 12.8); O_2, 62.1 years (SE 12.5). In Stub 2015, the median and interquartile range were 62 years (IQR 53.0 to 71.0) and 63.5 years (IQR 54.0 to 73.0) for the air and oxygen groups, respectively.

Intervention: in all five included trials the intervention was inhaled oxygen at 4 L/min to 8 L/min. Administration was by mask in four studies and by a nasal cannula in the other study (Ukholkina 2005). The comparator was air in four studies, breathed normally in the two open-label studies and given at 4 L/min to 6 L/min by facial mask in the double-blind study. In the remaining study, the comparison was titrated oxygen delivered by nasal prongs or mask adjusting the flow-rate to achieve an oxygen saturation of 93% to 96% (Ranchord 2012).

Outcomes: all five studies reported death. Stub 2015 explicitly measured pain, while Rawles 1976 and Wilson 1997 reported opiate usage (as a proxy for pain). Four studies included infarct size estimated by electrocardiogram mapping (ECG), biochemical markers such as creatine kinase (CK), troponin (I or T) or BNP. Finally, two studies estimated infarct size by MRI (Ranchord 2012; Stub 2015).

The main characteristics of the included studies are in Characteristics of included studies.

Excluded studies

Of the 162 excluded articles, 80 did not report original data, 38 were not RCTs, 20 were RCTs of interventions that were not relevant to our study; and 16 papers reported studies that had a different oxygen intervention (8 used hyperbaric oxygen; 6, aqueous oxygen; 1, oxygen associated with haemoglobin; and 1, oxygen combined with nitric oxide versus placebo for pain control). Three records were related to previously identified ongoing trials. Of the five remaining papers, four were related to an ongoing trial (register, protocol, and two proceedings of congress of NCT01787110), and the other one was the protocol of a nested ongoing trial (NCT02290080). The main characteristics of the excluded studies are in the table Characteristics of excluded studies.

Risk of bias in included studies

Allocation

Three studies provided no description of randomisation sequence generation (Rawles 1976; Ukholkina 2005; Wilson 1997), and we therefore judged this domain to be at unclear risk of bias. In Ranchord 2012, a random number sequence was generated by a computer programme. This study was undertaken in two centres and randomisation was not stratified by centre; nevertheless we judged this as being at low risk of bias. In Stub 2015, a computer-generated code into blocks of 10 was used (low risk of bias).

In four studies, allocation was concealed using numbered sealed envelopes (Ranchord 2012; Rawles 1976; Stub 2015; Wilson 1997), so we judged them as being at low risk of bias. Ukholkina 2005 did not report the method of allocation concealment, so we judged it as being at unclear risk of bias. In Ranchord 2012 (two centres) there is no description of how the envelopes were distributed to each centre, but we judged it to carry a low risk. In Stub 2015 trial allocation concealment was accomplished with externally numbered sealed envelopes (each block of 10). Three of these envelopes were carried in each ambulance and were replaced with the remainder envelops from the block. When the block was completed, a new block of 10 envelopes was allocated to the ambulance by the study coordinator. In terms of randomisation this may be seen as a strata for each ambulance (we judged this as being at low risk of bias).

Blinding

Only Rawles 1976 was double-blinded. Blinding was done by using shrouded cylinders, but there is no information about how effective this was. Nursing staff were not aware that the record of opiate administration would be used as a proxy measure of pain. The use of shrouded cylinders left blinding potentially compromised, so we could not rule out performance and observer bias and judged this domain as being at unclear risk of bias. However, while this could affect the assessment of the surrogate outcomes for pain, it is much less likely to have affected the primary outcome of this review, which was death (Wood 2008). We have no clear information whether infarct size measurement (through ECG, CK, troponin I, troponin T or BNP) was done blindly. In Ranchord 2012, the cardiologist who measured the infarct size through MRI was blinded to treatment received by the participant and to biomarker data. Finally in Stub 2015, there is no clear information on how investigators measured pain, but as this trial was open label, both patient and rater are unblinded; therefore we judged this to be at high risk of bias. Blind observers performed measurement of MRI offline on dedicated workstations; the statistician who analysed the data was blinded to the allocation, and a central coordinator blinded to treatment allocation performed the six-month clinical follow-up.

Performance and observer biases were possible in the four unblinded studies, which may have affected the direct measurement of pain in Stub 2015 and the surrogate outcome for pain in Wilson 1997, so we judged this as carrying a high risk of bias. Neither Ukholkina 2005 nor Ranchord 2012 reported this

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outcome. The assessment of the primary outcome (death) and the other secondary outcome of complications such as recurrent ischaemia or AMI, heart failure, arrhythmias and pericarditis were less likely to be subject to significant observer bias (we judged this as being at low risk of bias). On the other hand, the methods used for infarct size estimation (ECG, creatine kinase, troponin T, or MRI) are theoretically robust to observer bias, so these measures may be considered free of observer bias (low risk).

Incomplete outcome data

All participants were followed to discharge in Rawles 1976, but randomisation took place before confirming the diagnosis. AMI was not confirmed in 21.5% of participants with suspected AMI. Although this may appear high, it is not inconsistent with diagnostic techniques in the 1970s. Of the 105 people randomised to oxygen and the 95 to air, AMI was not confirmed in 25 and 18 participants, respectively. The characteristics of those in whom AMI was not confirmed were similar in both groups, and there were no deaths among the excluded individuals.

In Wilson 1997, it was unclear for how long participants were followed up. The analysis excluded eight people: one death, one stroke, four who withdrew consent and two because data were incomplete. This is 16% of the participants, and the expected effect on the results for the primary event was very low; the risk of bias was therefore high, but its direction is unknown.

In Ukholkina 2005, investigators measured the outcomes for 10 days and lost no participants to follow-up. However, trials provided no explicit data about the participants who were excluded postrandomisation because of failed revascularisation or the relative number of failed revascularisations in each group. The mismatch between the numbers reported in the tables and the text suggest that two participants may have been excluded from the air group and four from the oxygen group, but we cannot be certain. Consequently, we could not include these participants in the intention-to-treat analysis, and we think there is a high risk of bias for the outcomes we measured.

In Ranchord 2012, 12 participants were excluded after randomisation (four in the experimental group and eight in the control group). The published study did not report these participants' outcomes, which were excluded from the analysis. The reasons for withdrawal were: absence of formal consent (n = 5), incorrect initial diagnosis of STEMI (n = 2 acute pericarditis and n = 3 with normal coronary arteries), and cardiogenic shock (n = 2), which was an exclusion criterion for the study. The group to which these participants had been allocated was not reported.

We contacted authors to try and find out to which groups the 12 withdrawn participants had been allocated and their vital status, so that we could include them in an intention-to-treat (ITT) analysis. Although the authors replied, the information provided was contradictory and of limited value. Initially we were told that five people had been withdrawn because they did not consent and that the other seven had not been randomised. When we enquired further about this because it contradicted the published report, we were told that these seven had been randomised. Of concern to us was the fact that the distribution of their allocation to groups subsequently provided was not consistent with the numbers in the published trial report. The authors declined to provide the mortality outcomes for the participants who had alternative diagnoses, stating that "[a]lthough they are described as 'randomised and withdrawn' in the manuscript, they received no study treatment. For these reasons we are firmly of the view that these subjects should not be included in the mortality analysis." This failure to appreciate the nature of ITT analysis compounded our concerns raised by the inconsistencies in the allocation information. The authors felt unable to tell us the mortality status of the five participants who did not consent on the grounds that "if they have not consented then we can collect no further details about them". While we understand that trial-specific data could not be collected on these people, mortality can be known by public methods. However, we appreciate that others may judge this differently. The only information of use was that three participants who withdrew because they had normal coronary arteries were alive at the end of the study period.

The two cases excluded from the analysis by cardiogenic shock merit special comment. While cardiogenic shock was an exclusion criterion of the study, it is important to recognise that this is a dynamic clinical condition that is present on admission to hospital in only 29% of those who go on to develop this complication. The paper does not report whether the participants had cardiogenic shock when they arrived at the hospital or not. If cardiogenic shock developed after randomisation but before treatment, then the exclusion of these participants could bias the results since people with cardiogenic shock have a higher mortality rate. This illustrates the importance of ITT analysis.

As we were unable to include these participants in the ITT analysis because mortality data were withheld, we undertook a sensitivity analysis with a 'worst-case' scenario in which we tested the robustness of the current estimate by assuming that both participants received oxygen but died.

In Stub 2015, all the participants (N = 638) were followed to hospital discharge. However, as randomisation occurred in the ambulance, and informed consent was obtained verbally and then provided in writing at hospital, 14 people refused to participate in the study (6 in the oxygen arm and 8 in the air) after randomisation. Data about mortality at discharge are available from all randomised participants except those who refused to give informed consent (N = 624). We contacted authors to include this information in the analysis assuming that mortality is information that may be known by public methods (consistent with the above-mentioned argument).

In addition, 35 participants were excluded after randomisation for "protocol violations", but these violations are not specified in the publication, and one repeated enrollment was also excluded. We contacted authors, who informed us of these causes: non-study hospital (n = 28), chest pain for more than 12 hours (n = 12), oxygen given prior contact paramedics (n = 2), and hypoxaemia before enrolment (n = 3). In total, 588 participants were assessed for STEMI in emergency department: 470 of them were eligible for angiography, but STEMI was only confirmed in 441. The primary analysis was performed exclusively in confirmed STEMI. The 29 patients who underwent angiography but had other diagnoses were excluded from the analysis (17 in the oxygen arm and 12 in the air). There is no published information about the final diagnosis of these excluded patients. We contacted the author who informed us of the final diagnoses in the O_2 group: 5 NSTEMI, 3 pericarditis, 2 apical ballooning syndrome (takotsubo) and 6 other diagnoses;

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and in the air group: 2 NSTEMI, 2 pericarditis, 1 aortic dissection, 4 apical ballooning syndrome, and 3 other.

Of a total of 624 randomised participants, AMI (STEMI or NSTEMI) was confirmed in 471. This implies that in 24.5% of randomised patients, AMI was not confirmed. This may appear to be a high rate of misdiagnosis in contemporary practice but could be explained, at least partially, by initial assessment undertaken by paramedics rather than physicians – data for 'false' activation of the cardiac catheter laboratory for STEMI varies, but some studies report 28% to 36% of misdiagnoses for STEMI (Barnes 2013; McCabe 2012), suggesting diagnosis remains a challenge in the pre-hospital phase where exposure of paramedics to STEMI is infrequent. There is no specific information about mortality in the AMI group (STEMI and NSTEMI). We contacted the authors, and all-cause mortality in AMI (STEMI or NSTEMI) at discharge and at six months was available and is discussed below. Regarding six-month follow-up, 11 participants each were lost in the oxygen group and air group.

For the analysis of primary outcome in this trial, data of the peak troponin I were available in 200 of the 218 in the oxygen group and in 205 of 223 participants in the air group (data were missing in 18 participants in each group, or 8.3% and 8.7% of the total, respectively). Data on CK is reported for 217 of 218 participants in the oxygen arm and for 222 of 223 in the air group (0.45% and 0.44%, respectively). The impact of these lost data on effect estimation is probably low in the case of CK (low risk of bias) but unknown in the case of troponin I (high risk of bias). The loss of these data may be related to the absence of a central 'core lab' for enzymes in this multicentre study.This last point may also induce some doubts about the quality control of these variables, which are the primary outcome in the Stub 2015 trial.

There is no detailed information about missing values of the biomarkers (cTnI and CK) that were used to elaborate the respective area under curve (AUC). The study report states that when one or more values were missing, authors addressed it through a strategy of trapezoidal integration with multiple imputation using a Markov Chain-Monte Carlo simulation and sensitivity analysis. We judged this domain to be at unclear risk of bias.

Selective reporting

Protocols were unavailable for older studies. Rawles 1976 was the best-quality trial, and we believe that the report probably included all the prespecified variables. In Wilson 1997, the primary purpose was to look at the incidence and degree of hypoxaemia and the effect of oxygen on hypoxaemia, rather than this review's primary outcome of death; the participant who died was excluded from the analysis. Despite contacting the authors, we were unable to establish in which group the death occurred, and we could not include this study in the meta-analysis. We carried out a sensitivity analysis to assess the potential risk of bias.

In Ukholkina 2005, ECGs were mapped to estimate the surrogate outcome of infarct size, but only in a subset of 31 participants in the oxygen group; there was no information for the air group. We therefore believe that it is not possible to draw meaningful conclusions about infarct size. We do not think the pain and death outcomes were subject to selective reporting.

In Ranchord 2012 the infarct size, estimated by MRI, was undertaken in a small subgroup of 71 participants (selective reporting of subgroup). In addition, neither the protocol nor the trial report give any defined criteria on whether or not to perform MRI, so this analysis should be considered a non-randomised comparison. On the other hand, given that MRI was performed four to six weeks after AMI, this specific subgroup represents a cohort of survivors, which also needs to be taken into account in the infarct size comparison. We judged this study to be at high risk of selective reporting bias.

In Stub 2015, all patients "who were agreeable to travel to a core site for scanning" were invited for MRI, which was therefore performed in a self-selected subgroup of 139 participants: 65 in the oxygen group and 74 in the air group (selective reporting of subgroup).The self-selection implies that randomisation was broken and therefore the comparison of infarct size estimated by MRI is a non-randomised comparison, very sensitive to selection bias. On the other hand, MRI was performed six months after the STEMI; consequently the infarct size was estimated in a cohort of survivors. If we accept an association between infarct size and mortality, the comparison between oxygen and air will be biased towards the null hypothesis. We judged this study to be at high risk of selective reporting bias.

Other potential sources of bias

We did not identify any other biases in Rawles 1976 or Wilson 1997.

Ukholkina 2005 reported differences in infarct size between the two interventions, but the authors did not specify the time after symptoms onset when creatine phosphokinase M and B isoenzymes (MB-CPK) were measured; they were not measured at the same time in all participants. In addition, no information was provided about the consistency and validity of the method used to map myocardial damage (number and blinding of observers; reliability and repeatability of their measurements; whether there were disagreements and, if so, how these were resolved). While these methodological weaknesses call into question the reliability of the estimation of myocardial damage, they do not affect the main outcomes of this review. Only Ukholkina 2005 reported complications, but there was an inconsistency between the data in the table and the text. We recalculated complication rates and used these data in our analysis.

In Ranchord 2012, prior to randomisation both the experimental and control groups received pre-hospital oxygen (86.8% and 63.0%, respectively). If the effect of oxygen truly determines the outcome, then this pre-randomisation intervention could have produced a bias in effect estimation toward the null hypothesis (i.e. a reduction of the study power).

In Stub 2015, we detected some differences between the final paper and the published protocol. Firstly, the study population in the protocol is "suspicion of STEMI" but in the final paper the analysis was performed in confirmed STEMI (normoxic patients with STEMI). Secondly, there are differences in the sample size calculations despite using similar assumptions: in the protocol the estimated sample size was 490 (245 patients in each arm) while in the paper the sample size calculation was 600 participants, and 638 were enrolled. Finally, the protocol reported planning an interim analysis after randomisation of 100 participants in each arm, while in the paper the interim analysis was performed after 405 participants were recruited. In both cases justification for these number of patients to make the interim analysis is unclear, and there is no reflection about implications for the statistical analysis.

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It is difficult to know the possible impact on validity of these discrepancies between the paper and the protocol (unclear risk of bias). However it is clear that authors changed some decisions regarding the conduct of the study after commencing, and they did not adequately explain these decisions in the paper. This suggests that some decisions could have been 'data-induced' or motivated by post hoc hypotheses.

Baseline characteristics

Overall, the two groups appeared similar after randomisation in Rawles 1976 and Wilson 1997. In Ukholkina 2005 the two groups appeared similar in age, smoking, hypertension, unstable angina and cholesterol. There was a (non-significant) difference in the Killip stage, with more Killip II in the oxygen group than in the air group. Time to revascularisation was 41 minutes shorter in the air group (P = 0.052), which even if due to chance may have important clinical implications for our outcomes of interest. In Ranchord 2012 the two groups appear similar in age, sex, body mass index, diabetes, hyperlipidaemia, hypertension and previous coronary artery bypass grafting. There were differences in the number of previous percutaneous coronary interventions (PCIs), and in the infarct territory, with less anterior infarction in the experimental group than in the control group (18% versus 31%).

In Stub 2015 baseline characteristics are reported for 441 participants with STEMI confirmed by angiography. There was no clear difference between oxygen and air regarding important clinical characteristics. Surprisingly, there is no description of the baseline characteristics of all randomised patients according to table 1 of the CONSORT statement. Therefore we cannot make a judgement on whether the randomisation process worked, given that is not possible to explore the differences in potential confounding factors between randomised groups.

Summary of risk of bias

Death as an outcome had a low risk of bias in Rawles 1976 and Stub 2015, was not adequately reported in Wilson 1997, and had a high risk of bias in Ukholkina 2005. There are also the 'withdrawn' participants from Ranchord 2012, for whom we had no outcome data and do not know their vital status. We therefore consider the overall risk of bias for mortality in the meta-analyses to be high. For pain, we consider the risk of bias to be unclear in Rawles 1976 and high in Wilson 1997 and Stub 2015. Consequently we consider the risk of bias in the meta-analysis for pain to be high. For ischaemia recurrence there are low risks of bias in both Ukholkina 2005 and Stub 2015 (Figure 3).

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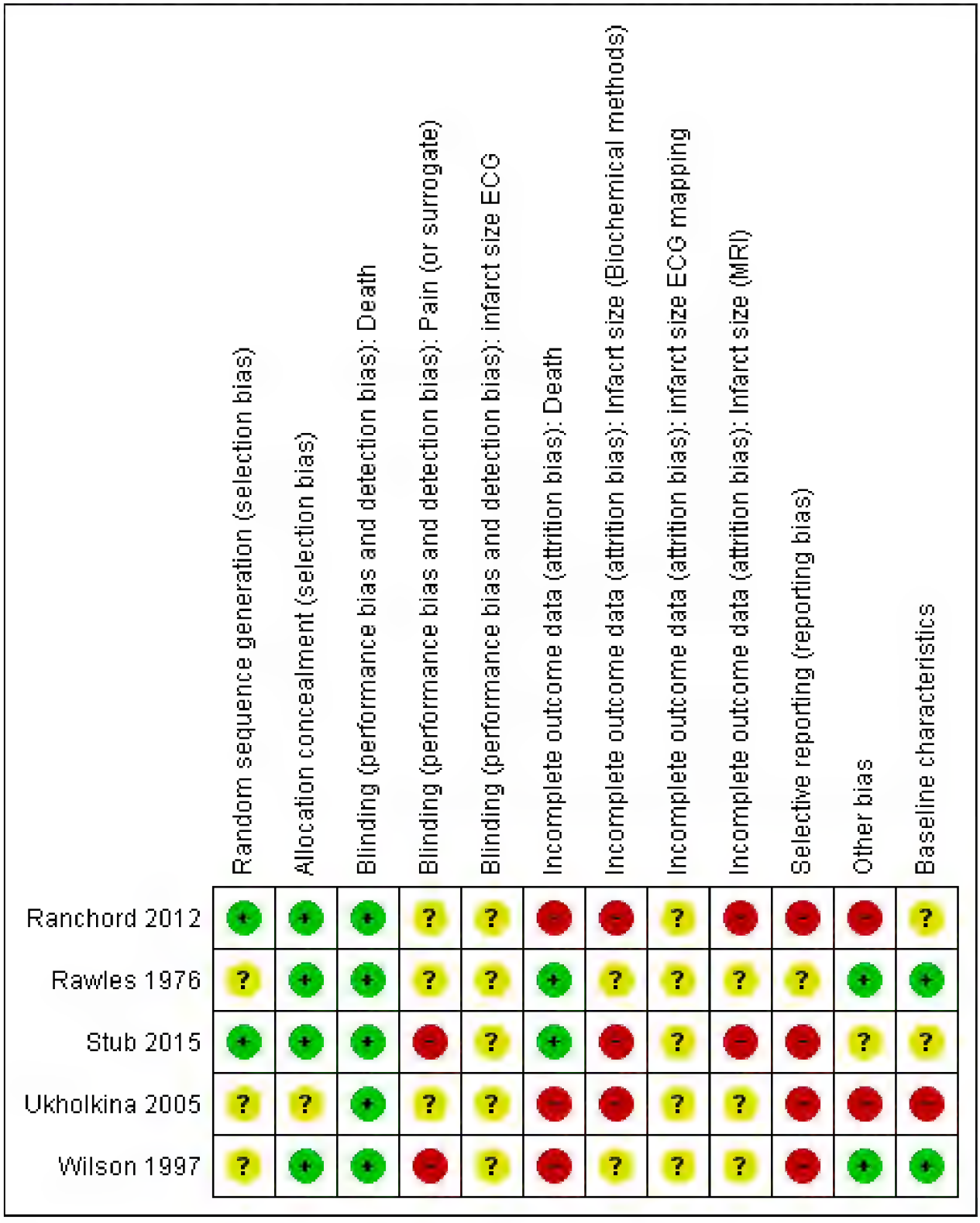
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias and detection bias): Death
Blinding (performance bias and detection bias): Pain (or surrogate)
Blinding (performance bias and detection bias): infarct size ECG
Incomplete outcome data (attrition bias): Death
Incomplete outcome data (attrition bias): Infacrt size (Biochemical methods)
Incomplete outcome data (attrition bias): infarct size ECG mapping
Incomplete outcome data (attrition bias): Infarct size (MRI)
Selective reporting (reporting bias)
Other bias
Baseline characteristics
Ranchord 2012
Rawles 1976
Stub 2015
Ukholkina 2005
Wilson 1997

For infarct size estimated by CK and MB, there is high risk of bias in Ukholkina 2005 and a low risk of bias in Stub 2015. For infarct size by different troponins the risks are unclear in Ranchord 2012 and Stub 2015. Finally, for infarct size estimated by MRI there is high risk of bias in both Ranchord 2012 and Stub 2015.

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Effects of interventions

See: **Summary of findings for the main comparison** Oxygen versus air for acute myocardial infarction

All-cause mortality

All five trials reported the observed mortality at hospital discharge. Rawles 1976 found more deaths in the group randomised to oxygen than in the air group, both for all randomised participants with suspected AMI (N = 200) and for those with confirmed AMI (N = 157). Wilson 1997 described one death but did not report in which group it occurred. We contacted both of the authors of the original paper, who confirmed that they no longer had the trial data and did not remember in which arm the death and the stroke had occurred; however, they stated that 25 participants had been randomised into each group. In Ukholkina 2005, only 1 person out of 58 died in the oxygen group and none out of 79 participants died in the air group. In Ranchord 2012 ,1 participant out of 68 died in the high oxygen group and 2 out 68 in the titrated group. Twelve participants (4 in the high oxygen group and 8 in the titrated group) were withdrawn after randomisation, with the mortality data for these 12 people not reported in the paper. We contacted the authors of the trial, but they were unable to provide the missing data for these cases. In Stub 2015 the all-cause mortality at discharge was 4 out 218 and 10 out 223, respectively, for the oxygen and air groups in confirmed STEMI, and 5 out 231 and 11 out 240 respectively for the AMI (STEMI or NSTEMI).

We could only combine results from four of the five studies (Ranchord 2012; Rawles 1976; Stub 2015; Ukholkina 2005). In contrast with previous versions of this review, in the meta-analysis of the current version, the same number of people died (n = 16) in each group . This suggests oxygen effect is not good, but not harmful. The complete results are given numerically below together with the GRADE assessment in the Summary of findings for the main comparison (Guyatt 2008).We also present the sensitivity analysis for the missing data from Wilson 1997 and Ranchord 2012 .

Meta-analysis for mortality in participants with confirmed AMI: risk ratio (RR) 1.02 (95% CI 0.52 to 1.98); I^2 = 49%, fixed-effect model; 4 trials, N = 871, quality of evidence: very low (Analysis 1.1). The effect does not change when applying a random-effects model (Analysis 1.2).

Meta-analysis for mortality in an ITT population, including those who did not have AMI showed an RR of 0.99 (95% CI 0.50 to 1.95; I^2 = 46%, fixed-effect model; 4 trials, N = 1123, quality of evidence very low; Analysis 1.3). The effect does not change when applying a random-effects model (Analysis 1.4).

Sensitivity analysis for missing information about the arm in which the death occurred in Wilson 1997 (ITT analysis): a 'worst-case' scenario assuming that the participant who died was in the oxygen arm gave an RR for death of 1.05 (95% CI 0.54 to 2.02; I^2 = 33%; fixed-effect model; 5 trials, N = 1173; Analysis 1.5). A 'best-case' scenario assuming that the participant who died was in the air arm gave an RR for death of 0.94 (95% CI 0.49 to 1.80; I^2 = 32%; 5 trials, N = 1173; Analysis 1.6). In both cases we used a fixed-effect model. Sensitivity analysis for missing information about the group in which the two participants of Ranchord 2012 with cardiogenic shock were allocated: assuming that both participants died, a 'worst-case' scenario in which both were in the oxygen arm gave an RR of 1.11 (95% CI 0.58 to 2.15; I^2 = 45%; 4 trials, N = 1123; Analysis 1.7) and a 'best-case' assuming that the participants were in the control arm gave a RR of 0.89 (95% CI 0.046 to 1.71; I^2=54%; 4 trials, N = 1123; Analysis 1.8).

The subgroup analysis, including only the three most recent trials, all which were performed in the reperfusion era (Analysis 1.9), gave an RR for death of 0.58 (95% CI 0.24 to 1.39; I^2 = 0% fixed-effect model; 3 trials, N = 923, quality of evidence: low). Despite being recent, two of these three studies did not meet current standards of trial design and conduct and are at high risk of bias (see Risk of bias in included studies).

Only Stub 2015 reported all-cause mortality at six months: 9 participants out 318 died in oxygen group versus 13 out 320 in the air group (RR 0.39, 95% IC 0.14 to 1.07; 1 trial, N = 628).

Cardiac mortality

Only Stub 2015 reported cardiac mortality, with 4 out 318 and 7 out 320 participants dying in the oxygen and air groups, respectively (RR 0.58, 95% CI 0.17 to 1.95; 1 trial, N = 628).

Cardiac failure

Two studies reported cardiac failure (Rawles 1976; Wilson 1997). In Ranchord 2012, cardiogenic shock was an exclusion criterion for the study, so the two cases that occurred postrandomisation were excluded from the analysis. In Ukholkina 2005, cardiogenic shock and cardiac failure at hospital arrival were also considered criteria for exclusion from the trial. In included participants, cardiac failure was reported in one and five participants in the oxygen and air groups, respectively. In Stub 2015, 20 participants in each group presented cardiogenic shock. The meta-analysis for cardiac failure showed no significant difference between groups (RR 0.88, 95% CI 0.50 to 1.55; I^2 = 27%, 2 trials, N = 775; Analysis 1.10).

Stroke

Only one trial reported stroke or transitory ischaemic attack, which occurred in 3 out 218 participants in the oxygen group and and 1 out 223 in the air group (Stub 2015).

Recurrence of myocardial infarction or ischaemia

Recurrence of ischaemia was similar in both groups in Ukholkina 2005: it occurred in 12 participants in the oxygen group (N=58) and 16 (N= 79) in the air group (RR 1.02, 95% CI 0.52 to 1.99; 1 trial, N = 137). Conversely in Stub 2015, recurrence of myocardial infarction or ischaemia at hospital discharge occurred in 12 out 218 participants in the oxygen group and in 2 out 223 in the air group (RR 6.14, 95% CI 1.39 to 27.1), which suggests a negative effect for oxygen. The effect estimate from both studies suggests a disadvantage for oxygen, but this is not significant: meta-analysis of the two trials shows an RR of 1.67 (95% CI 0.94 to 2.99; I^2= 80%, 2 trials, N = 578, quality of evidence: low; Analysis 1.11). This substantial heterogeneity could be due to different causes. In Ukholkina 2005, inclusion criteria were uncomplicated AMI, exclusion criteria included cardiogenic shock, and failure in revascularisation was considered cause for study withdrawal. Moreover, the study setting was clearly different: participants in Ukholkina 2005 were recruited in hospital, versus pre-hospital in Stub 2015 (methodological sources of heterogeneity). On the other hand, part of the observed heterogeneity may be

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related to technological and procedural advances in percutaneous intervention (stenting, thromboaspiration, etc.) and with progress in the use of adjuvant antiplatelet medication in the decade separating the two trials (clinical sources of heterogeneity). Finally, some heterogeneity may be statistical.

Recurrence of myocardial infarction at six months in Stub 2015 occurred in 16 (out 218) and 8 (out 223) participants in the oxygen and air groups respectively (RR 2.05 [95% CI 0.89 to 4.68] 1 trial, N=441)

Major bleeding

Stub 2015 was the only trial to report major bleeding: 9 and 6 cases were reported in the oxygen (n = 218) and air groups (n = 223), respectively (RR 1.53, 95% CI 0.56 to 4.24, 1 trial, N = 441). In two cases in the air group, this outcome was the cause of death.

Pain

Stub 2015 directly measured pain at two time points: on arrival of paramedics and on arrival at hospital. The median pain scores were exactly the same for both the oxygen and air groups in both measurements: median 6.0 (IQR 4.8 to 8.0) versus 6.0 (IQR 4.0 to 8.0) on arrival of paramedics, and 2.0 (IQR 0.0 to 4.0) versus 2.0 (IQR 0.5 to 3.5) on arrival at hospital.There is not explicit description of the used tool for this measurement (probably a 10-point VAS scale). In two other studies, the authors reported diamorphine use as a proxy for pain: in Rawles 1976, a similar proportion of participants from both groups received analgesia. The total dosage was similar: 54.3% of randomised participants (71.3% of those with confirmed AMI) in the oxygen group received analgesia, with an average of 2.1 doses (standard deviation (SD) 1.5), but it was not clear whether the denominator was participants who used diamorphine or all participants; 54.7% of randomised participants (67.5% of those with confirmed AMI) in the air group received analgesia, with an average of 2.0 doses (SD 1.4), but again the denominator population was not clearly defined. In Wilson 1997, the authors reported opiate use as a proxy for pain. Although 50 people were randomised, authors reported results for just 42, as follows: 16 of 22 participants (72.7%) in the oxygen group used opiates; 18 of 20 participants (90%) in the air group used opiates. Ukholkina 2005 did not measure pain or opiates use.Thus, we can only combine results from two studies (Rawles 1976; Wilson 1997), which showed no difference in opiate use between the oxygen and the air groups. Meta-analysis for opiate use in confirmed AMI showed the following results (fixed-effect model): RR 0.99 (95% CI 0.83 to 1.18; I^2 = 54%, 2 trials, N = 190, quality of evidence: low; Analysis 1.12). Applying a random-effects model slightly altered these results: RR 0.94 (95% CI 0.72 to 1.23; I^2 = 54%, 2 trials, N = 190; Analysis 1.13). Meta-analysis for opiate use in the ITT population including those who did not have an AMI (fixed-effect model): RR 0.97 (95% CI 0.78 to 1.20; I^2 = 0%, 2 trials, N = 250, quality of evidence: low; Analysis 1.14). This remained unchanged using a random-effects model: RR 1.04 (95% CI 0.78 to 1.38; I^2 = 0%; Analysis 1.15).

Revascularisation

Revascularisation (as the current standard of the treatment in AMI) was a criteria for inclusion in the three most recent trials (Ranchord 2012; Stub 2015; Ukholkina 2005). Only Stub 2015 reported 'new' revascularisation as an outcome. Twenty-three of 218 participants in oxygen group and 16 of 223 in the air group underwent revascularisation. There is no information about the causes of new revascularisation nor of the techniques used for it.

Pericarditis

Only Ukholkina 2005 reported pericarditis as a complication of AMI: 1 participant in the oxygen group (n = 58) and 6 participants in the air group (n = 79) experienced this outcome. Stub 2015 randomised and included 15 cases of acute pericarditis in the study as AMI (9 in the oxygen and 6 in the air group). The true diagnosis was made after catheterisation, leading to these participants' exclusion from the study analysis. However, we have included these participants in the ITT analysis.

Arrhythmia

Four trials reported different types of arrhythmias, but the information is not detailed enough to make a qualitative syntheses (Rawles 1976; Stub 2015; Ukholkina 2005; Wilson 1997).

Left ventricular function

Three studies estimated ventricular function using different imaging techniques (echocardiography, MRI) (Ranchord 2012; Stub 2015; Ukholkina 2005). Investigators performed measurements at different points of AMI clinical evolution, and given the dynamic condition of this outcome in AMI, the variability in considered time points may be an important source of variability in the results. Thus, we did not attempt any synthesis for this outcome.

Infarct size estimation

Four of the five studies explored the effect of oxygen on infarct size using different methods (Ranchord 2012; Rawles 1976; Stub 2015; Ukholkina 2005).

In the oldest trial (Rawles 1976), investigators estimated infarct size by means of maximum serum aspartate aminotransferase levels. In two other studies, authors used CK or CK-MB (peak or AUC): in Ukholkina 2005, CPK and MB-CPK activity was significantly higher in the oxygen arm at 6 hours and 24 hours of symptoms onset, while at other time points of the clinical evolution (between 12 and 18 hours, as well as at 36 and 48 hours after onset) the levels of MB-CPK and CPK were significantly lower in the oxygen group. The authors considered this ambiguous result to be favourable to oxygen but provided no coherent explanation for these data. Stub 2015 found a significant increase in the geometric mean peak of creatine kinase in the oxygen group compared with the non-oxygen group (1948 U/L versus 1543 U/L; geometric means ratio 1.27, 95% CI 1.04 to 1.52). There was a similar result when using the AUC: ratio of geometric means of AUC 1.19 (95% CI 1.01 to 1.40). Given the huge differences in the timing of blood sampling, in laboratory methods and in mathematical expression, it was not possible to make quantitative syntheses of infarct size by CK. On the other hand, the two more recent trials measured different subtypes of troponin. In Ranchord 2012, the mean ratio of troponin T in the oxygen versus air group was 0.74 (95% CI 0.50 to 1.10), and in Stub 2015, the mean ratio of troponin I between oxygen and air was 1.20 (95% CI 0.92 to 1.56); no significant differences were apparent in either case. It was not possible to undertake meta-analysis of infarct size by troponin. The quality of evidence for this outcome was low.

In two studies, MRI was used to estimate infarct size (Ranchord 2012; Stub 2015). In Ranchord 2012, the mean infarct size was 15.6 g (SD 15.6) in the oxygen group and 16.3 g (SD 11.7) in the air group.

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The mean difference of infarct mass between oxygen and air groups was −0.8 g (95% CI −7.6 to 6.1). When expressed as a percentage of left ventricular mass, mean infarct mass was 12.5% (SD 10.9) in oxygen versus 13.1% (SD 9.7) in the air group, which suggests a positive (but not significant) effect for oxygen. However, in Stub 2015 the geometric mean of infarct mass was 14.6 g (IQR 11.3 to 18.3) in the oxygen group versus 10.2 g (IQR 7.7 to 13.4) in the air group, and the ratio of geometric means of infarct size was 1.43 (95% CI 0.99 to 2.07), which suggests an increase of infarct size in the oxygen group on the border of statistical significance. When expressed as a percentage of infarct mass, the geometric mean was 12.6% (IQR 6.7 to 19.2) in the oxygen group and 9.0% (IQR 4.1 to 16.3) in the air group. It is clear that these indices have different mathematical properties (we contacted authors). Nevertheless, considering that these comparisons come from biased subgroups of patients of the trials, we considered them unsuitable to make quantitative synthesis of infarct size estimated by MRI. The quality of evidence for this outcome is very low.

DISCUSSION

Summary of main results

We identified five studies meeting our inclusion criteria, involving a total of 1173 participants, 32 of whom died. The quality of the evidence, according to GRADE, ranged from low to very low (Guyatt 2008). There were a similar number of deaths in people receiving oxygen versus air, so for all-cause mortality at hospital discharge there is neither evidence of benefit nor harm for oxygen treatment in patients with AMI. This finding is consistent in the intention-to-treat meta-analysis and the confirmed AMI meta-analysis. Interestingly, the inclusion of the recent Stub 2015 trial changed the RR from our previous review, where the ITT analysis gave an RR of 2.05 (95% CI 0.75 to 5.58), compared to 0.99 (95% CI 0.50 to 1.95) in the present review. In confirmed AMI, the RR changed from 2.11 (CI 0.78 to 5.68) to 1.02 (CI 0.52 to 1.98).

Regarding pain, there was no effect for oxygen on pain relief when pain was directly measured nor when trials measured opiate use as a surrogate for pain. With regard to complications following AMI, there was no clear effect for oxygen on a range of complications, except for recurrent ischaemia, which was higher (but not significantly so) in the oxygen group compared to the air group.

Based on outcomes that were 'important but not critical for decision-making', particularly infarct size, there was partial evidence that oxygen may increase infarct size as estimated by CK. However, this evidence is not consistent with CK in other trials and is also inconsistent when infarct size is estimated through troponin I or T (even when CK and troponin I were measured in the same trial). Finally, there is no evidence of effect for oxygen on infarct size as estimated by MRI.

Overall completeness and applicability of evidence

Regarding the applicability of the evidence, three aspects are worth noting.

Firstly, Rawles 1976 took place before the reperfusion era (primary percutaneous coronary intervention (PPCI) or thrombolysis) and also before the routine use of treatments such as beta-blockers, aspirin, angiotensin-converting enzyme inhibitors or modern antiplatelet therapies, so their results may have been different in today's context. The sensitivity analysis for death in the reperfusion era trials gave moderate quality of evidence; nevertheless, readers should consider the resulting risk ratio (RR) of 0.58 (95% CI 0.24 to 1.39; I^2 = 0%; 3 studies, N = 913) when planning future studies (for example, in calculating sample sizes).

Moreover, the reported case fatality rates from AMI have fallen in recent decades (Koopman 2013; Schmidt 2012; Smolina 2012; Yeh 2010). In the studies included in this review, hospital mortality among control participants was only 3.8%. This rate is lower than that observed in routine surveillance data (Babaev 2005; Movahed 2009), and it is half that of the recent Euro Heart Survey in 47 countries, where hospital mortality was 6.2% (Puymirat 2013). A possible explanation is that these trials only recruited lower-risk participants, but it there could have also been a chance deficit of deaths in the control arm, which would have contributed to the apparent difference between the oxygen and control groups. This aspect should inform participant selection criteria in future studies.

The the most recent trial had a large impact on our estimation of all-cause mortality. However, all cases of non-cardiac mortality were in the air group (3 out 11: 27%), and three deaths were due to complications presumably unrelated to oxygen: major bleeding in two cases and sepsis in the other. In a sensitivity analysis, if these 3 cases had occurred in the oxygen group, the RR for the ITT meta analysis would have been 1.43 (95% CI 0.72 to 2.84), instead of 0.99 (95% CI 0.50 to 1.95). Similar change is apparent in the subgroup of participants in the reperfusion era: from RR 0.58 (95% CI 0.24 to 1.39) to RR 1.04 (95% CI 0.45 to 2.41).

Secondly, despite the longstanding beliefs of health professionals, there is no evidence that oxygen has a beneficial effect on pain, whether measured directly or by proxy variables. This result is consistent with a new trial undertaken with oxygen versus air during percutaneous coronary intervention for balloon-induced angina (Zughaft 2013), which we considered but excluded from this review.

A further issue to consider when assessing the contemporary relevance and applicability of the earlier studies in our review is that the definition of AMI has evolved over the years to reflect increasing understanding of underlying pathophysiological processes as well as developments in diagnostic techniques such as the high sensitivity troponins. Furthermore, there is now recognition that acute coronary syndromes represent a spectrum of pathophysiological processes rather than a uniform type of 'heart attack'. Notably, there are now separate guidelines for STEMI and NSTEMI presentations, reflecting the different therapeutic options. Future studies should consider this spectrum of ACS, as mortality varies by phenotype (at least in the hospital stay), but in clinical terms the common scenario for decision-making about oxygen administration is at the point where AMI is suspected, regardless of final diagnosis following biomarker of coronary angiography.

Bearing these considerations in mind, future studies of oxygen in (suspected) AMI should enrol participants in the pre-hospital phase. Given the challenges of pre-hospital diagnosis, this probably implies (as in Stub 2015) that trials will recruit a significant proportion of participants without a subsequent confirmed diagnosis of AMI. To minimise this problem, some ongoing trials are using wireless ECG transmission with interpretation by cardiology staff and additional discussion of the patient. In any case, for

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mortality and some other variables, it is possible to make a true intention-to-treat (ITT) analysis, but assessing other clinical outcomes such as infarct size or complications may not be practical or appropriate for all randomised patients. The optimal time for estimating infarct size for clinical research using MRI is worthy of special consideration.

Quality of the evidence

The (published and unpublished) evidence in support of such a widespread practice is surprisingly scant and scattered. We used the GRADE approach to assess the quality of evidence and the GRADE profiler (GRADEpro) to import data from RevMan to create 'Summary of findings' tables (GRADEpro; RevMan 2014).The quality of evidence for the outcomes judged critical for decision-making was very low for death and low for pain and for recurrent ischaemia. Therefore, with regard to these outcomes, readers should interpret results with caution (Summary of findings for the main comparison).

Oxygen trials have rarely investigated – and poorly reported – different complications such as cardiac failure, bleeding, stroke, recurrence of ischaemia, pericarditis, etc. Despite being hard variables that are robust to observed bias, these outcomes are not totally free of performance bias, and quality of the evidence is low or very low, meriting caution upon interpretation.

Finally, for other outcomes judged 'important but not critical for decision-making', such as infarct size measured by biological markers, the quality of evidence is low, and very low in the case of infarct size estimated by MRI.

Potential biases in the review process

We were unable to determine if there was any publication bias using formal methods, as we found only five studies for inclusion. We cannot rule out the possibility that there are unpublished or ongoing studies, especially in languages other than English, that were not indexed in the electronic databases we searched.

Regarding heterogeneity, in the meta-analysis for opiate use in confirmed AMI, we found moderate heterogeneity ($I^2 = 54\%$), which disappeared in the ITT analysis. While the two studies used in the meta-analysis had differences in their design (for example, blinded versus open-label) and attrition rates (much higher in Wilson 1997), it was not possible to investigate the heterogeneity further with only two trials.

Agreements and disagreements with other studies or reviews

The findings of our updated review are not consistent with prior reviews (Cabello 2010; Cabello 2013), and the inclusion of a new trial has altered the evidence (point estimate) of the previous version of this review, which suggested an excess of mortality in the oxygen group compared to air (Stub 2015). Nevertheless, the results of this updated review are too imprecise to definitively determine whether oxygen is helpful or harmful in AMI.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence available about the effect of the oxygen on all-cause mortality in patients with AMI is inconclusive, and we cannot rule out a possible harmful effect. This lack of evidence is consistent across different outcomes critical for clinical decisions. However, the evidence in this area is sparse, of low or very low quality, and partially predates the advances in reperfusion techniques and trial methods of recent years. Finally, the evidence about the effects of oxygen on other type 2 outcomes such as infarct size (estimated through different methods) is also inconsistent and of very low quality.

Therefore, current evidence neither supports nor clearly refutes the routine use of oxygen in people with AMI. The implication for clinical practice is that pending new evidence, practitioners should only give oxygen to patients with suspected or confirmed AMI with a blood oxygen saturation < 90% or in cases of patients with respiratory distress.

Implications for research

As early as 1950, studies demonstrated that the administration of pure oxygen via a facial mask not only failed to reduce the duration of angina pain but also prolonged the electrocardiographic changes indicative of an AMI (Russek 1950). In 1975, other authors explicitly called for further research on the topic (Salzman 1975). Given that Rawles 1976 subsequently suggested possible harm, it is surprising that no research groups have undertaken a definitive study to rule out the possibility that oxygen may do more harm than good. The recently published Stub 2015 has reactivated clinical and scientific interest in the possible harmful effects of oxygen (Nedeljkovic 2015).

Part of the reason for the failure to fund such an essential study until recently may be the strong assumption (Cabello 2009; Danchin 2009), based on pathophysiological reasoning, that oxygen administration reduces both the oxygen deficit in ischaemic myocardial tissue and consequent tissue death. Indeed, both the medical profession and the public have become so familiar with the use of oxygen that the general attitude may have been that even if oxygen does no good, it is at least not harmful. However, recent years have seen the recognition of oxygen as a 'vasoactive substance' (Farquhar 2009). In summary, while there are pathophysiological reasons to believe that oxygen may have the potential to reduce tissue damage, it is also biologically plausible that oxygen is doing harm (see Why it is important to do this review).

Given the widespread use of oxygen for AMI, the inconsistencies in recommendations about when and to whom it should be given, and the fact that the best current evidence is not conclusive regarding benefit or harm, we maintain the belief expressed in our previous reviews that there is an urgent need for an adequately powered randomised controlled trial to establish the effects of administering oxygen to people with AMI. That trial must incorporate contemporary standards in design, conduct, analysis and reporting of trials and address the spectrum, population and sample size mentioned above to reflect contemporary diagnosis and care of the patient with AMI.

Three of the identified ongoing trials are currently recruiting participants (NCT01787110; NCT02290080; NCT01423929). The first is an ambitious trial (DETOX-AMI) based on the national AMI registry in Sweden, focused on mortality and recruiting in the pre-hospital phase of AMI, with a planned sample size of 6000 participants. This trial has a nested sub-study focused on biological markers. A third nested study is focused on the effect of oxygen on infarct

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size estimated by biochemical markers and MRI in patients with STEMI. The MRI study will be performed at two to six days of AMI to determine the myocardium at risk and to calculate the myocardial salvage index (MSI) by PCI.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ranchord 2012

Methods	Open-label randomised controlled trial (6 weeks)
Participants	People with ischaemic symptoms + ST-segment elevation (0.1 mV) in 2 contiguous leads STEMI or elevation (0.2 mV) in more than 2 precordial leads (STEMI), or with ischaemic symptoms + new onset left bundle branch block N randomised = 148. N analysed = 136. Dropouts: withdrew consent (n = 5), alternative diagnosis (n = 5): 2 cases with pericarditis and 3 cases with normal coronary arteries. 2 cases of cardiogenic shock (an exclusion criterion) Mean age (SD): oxygen 60 years (12.5), air 60 years (12.8). Sex: 77.9% men in oxygen and 70.6% men in air group
Interventions	Intervention: oxygen high flow 6 L/min by concentration mask Comparator: oxygen titrated delivered by nasal prongs or mask adjusting the flow-rate to achieve an oxygen saturation of 93%-96%
Outcomes	30 days mortality, complications, infarct size estimated by troponin T level measured 66 h to 78 h after randomisation, infarct mass (absolute and as percentage) documented by MRI (measured at 4-6 weeks after AMI in a subset of participants), pro-BNP measured 24 h after randomisation. As composite variable, major cardiac event (death, reinfarction, target vessel revascularisation) at 30 days
Exclusions	Previous myocardial infarction, COPD, type II respiratory failure, cardiogenic shock, oxygen desaturation below 85%, pregnancy, bleomycin treatment or participation in another trial
Length of follow-up	30 days for mortality, troponin T and BNP, 4-5 weeks after AMI for MRI
Clinical Context and parallel care	The study was undertaken exclusively in inpatients, therefore the pre-hospital phase of AMI was not considered. Primary percutaneous coronary intervention (PPCI) was the first-choice treatment in one centre, while in the other, PPCI or thrombolysis was the treatment, depending on the hour of hospital admission.
Notes	The study was conducted in two centres.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sequence was undertaken by a computer programme.
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias)	Low risk	There is no threat for this outcome

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Ranchord 2012 *(Continued)*

Death		
Blinding (performance bias and detection bias) Pain (or surrogate)	Unclear risk	Not applicable in this trial
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Death	High risk	There are 12 postrandomisation exclusions for which there are no 30-day mortality data reported.
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	High risk	There are 12 postrandomisation exclusions in which there are no reported biochemical data
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Infarct size (MRI)	High risk	By definition, the primary outcome (30 days mortality) implies that MRI was not performed (by protocol performed 4-5 weeks after AMI). Data therefore not available.
Selective reporting (reporting bias)	High risk	MRI was performed only in a subgroup of participants (selective reporting of subgroup)
Other bias	High risk	Pre-randomisation oxygen was administered in experimental and control group (86.8% and 63% respectively). This prerandomisation intervention may have produced a bias in effect estimation towards the null hypothesis. The comparison of infarct size measured by MRI between the two groups should be considered a non-randomised comparison, therefore prone to the bias of observational studies
Baseline characteristics	Unclear risk	There were differences in previous PCI, and in the infarct territory: anterior infarction was less frequent in the experimental group (18%) than in the control group (31%)

Rawles 1976

Methods	Double-blind, randomised controlled trial (In-Hospital period)
Participants	People with suspected AMI presenting within 24 h of symptoms onset Clinical setting: single site coronary care unit in the UK N randomised = 200: 105 oxygen and 95 air. N analysed: 80 oxygen and 77 air Excluded (non-confirmed AMI): 25 oxygen and 18 air Mean age (SD): oxygen 51.3 years (1.7), air 50.8 years (2.4) Sex: 60% men in oxygen and 64% in air group

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Rawles 1976 *(Continued)*

Interventions	Oxygen or compressed air administered by MC mask at 6 L/min over 24 h Comparator: air at normal pressure given at 6 L/min by MC mask
Outcomes	Death in Hospital, arrhythmias in 24 hours, use of opiates, maximum serum aspartate aminotransferase levels, length of stay, systolic ejection time, hypoxaemia (first day)
Exclusions	People with heart failure, bronchitis, emphysema, or other respiratory problems
Length of follow-up	Discharge
Clinical Context and parallel care	Prethrombolysis period
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was no description of how the sequence was generated
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes
Blinding (performance bias and detection bias) Death	Low risk	Double-blinded using shrouded cylinders (but likely that the blinding could have been compromised)
Blinding (performance bias and detection bias) Pain (or surrogate)	Unclear risk	Double-blinded using shrouded cylinders (but likely that the blinding could have been compromised, and this may affect the assessment of this outcome: pain or surrogate)
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Death	Low risk	There were postrandomisation exclusions due to unconfirmed AMI (19% air group and 24% O_2 group)
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	Not applicable in this trial
Selective reporting (reporting bias)	Unclear risk	There was no protocol published, but we judged that there was no bias in reporting the primary outcome.

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Rawles 1976 *(Continued)*

Other bias	Low risk	We did not identify other biases.
Baseline characteristics	Low risk	Consecutive participants, similar age, sex

Stub 2015

Methods	Multicentre, open-label, randomised controlled trial (6 months)
Participants	Patients ≥18 year old with ischaemic symptoms of < 12 h duration, with evidence of STEMI defined by ST elevation > 0.1 mm in 2 contiguous limb leads, > 0.2 mm in 2 contiguous chest leads, or new left bundle branch block. In the published protocol the participants were defined as those with suspected STEMI. The recruitment was made in the pre-hospital setting (by paramedics in the ambulance) and the informed consent was obtained after the arrival at hospital (delayed consent) N randomised = 638. N analysed = 441: 14 refused consent, 35 exclusions for protocol violations, 1 repeated enrollment (see text). Elegible for angiography: 470 (471 for authors), 29 other diagnosis. Mean age (SD): oxygen 13.0 years (11.9), air 62.6 years (13.0) Sex: 79.8% men in oxygen, 78.0% men in air group
Interventions	Intervention: oxygen by mask 8 L/min Comparator: air If the oxygen saturation fell below 94% then titrated oxygen was administered by cannula or face mask to achieve an oxygen saturation of 94%.
Outcomes	Infarct size estimated by cTnI and CK (in both cases geometric mean peak and geometric mean of AUC) at 72 h of reperfusion Pain score (measured on arrival of paramedics and on arrival at hospital). The scale for measuring pain is not described in the protocol nor in the paper. Survival at hospital discharge, mortality and major adverse cardiac events (MACE: death, recurrent myocardial infarction, repeat revascularisation, and stroke) were assessed at 6 months Infarct size was estimated by MRI at 6 months after hospital discharge. An MRI was undertaken in a subset of self-selected participants (non-random comparison) *All primary efficacy and safety outcomes (mortality , cardiac arrest and unplanned intubation) were explored by a monitoring committee in an interim analysis made after 450 randomisations. In the protocol this interim analysis was planned after 100 were randomised to each arm. This planned analysis is not reported, and no adjustments for multiple comparisons were undertaken.
Exclusions	Oxygen desaturation < 94% (pulse oximeter); bronchospasm requiring salbutamol nebulised; altered conscious state; oxygen administration prior to randomisation
Length of follow-up	6 months
Clinical Context and parallel care	Primary percutaneous coronary intervention (PPCI) was the first-choice treatment in all the participant hospitals. All the patients received aspirin 300 mg in ambulance and antiplatelet therapy according to interventional cardiologist criteria.
Notes	This was a multicentre study undertaken in 9 metropolitan hospitals that provide 24 h percutaneous coronary intervention services.

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Stub 2015 *(Continued)*

The participant were included, randomised and treated (with oxygen or air) before the arrival at hospital (in the ambulance), and therefore the trial was designed to cover the pre-hospital phase of STEMI.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sequence was computer-generated code in blocks of ten.
Allocation concealment (selection bias)	Low risk	Sealed envelopes in each ambulance participating in the study: 3 envelopes of the block of 10, and replaced with other of the block, and after new block by coordinator.??
Blinding (performance bias and detection bias) Death	Low risk	There was no information in the paper about participants who refuse to give informed consent and we contacted the authors for more information.
Blinding (performance bias and detection bias) Pain (or surrogate)	High risk	This was an open label trial, although pain scores are shown, there is no description of the scale and methods used to measure the pain.
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Death	Low risk	Mortality at discharge and six month following the patient's randomisation
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	High risk	Peak of creatin kinase is reported in 217 of 218 participants in oxygen arm and in 222 of 223 in the air (loss of 0.45% and 0.44% respectively). Low risk of bias Peak of troponin I is reported in 200 of the 218 in the oxygen group and 205 of 223 participants in the air (loss of 8.3% and 8.7% respectively). High risk of bias The missing values in serial enzyme estimation to built the AUC are unknown (a method is described as a Markov method was used to performed the estimation of AUC. Unclear risk of bias
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Infarct size (MRI)	High risk	The MRI was done in a self-selected group of study population, this implies the existence of high risk of selection bias and the nullification of the balancing effect of randomisation.
Selective reporting (reporting bias)	High risk	MRI was performed only in a subgroup of 'self-selected' participants (selective reporting of subgroup) In addition, the MRI was undertaken 6 months after the STEMI and the population represents a cohort of survivors.
Other bias	Unclear risk	Protocol deviation, sample size, interim analysis
Baseline characteristics	Unclear risk	There is a table with the description of key data in both groups with confirmed STEMI, but there is no table comparing the baseline characteristics of all randomised patients (table 1 of CONSORT)

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Ukholkina 2005

Methods	Randomised, open-label, controlled trial (10 days)
Participants	Confirmed AMI within 12 h of onset of symptoms. Clinical setting: single-site coronary care unit in Russia N randomised = 137. No explicit data were provided about the participants who were excluded post-trandomisation Mean age (SD): oxygen 55.6 years (1.33), air 53.5 years (1.06) Sex: 45% men in oxygen and 70% in air group
Interventions	Oxygen for 3 h after intervention administered via nasal cannulae 3-6 L/min (FiO_2 30%-40%) and 30 min before the PCA in a subgroup of 30 participants Comparator: air
Outcomes	Death, arrhythmias within 1 h of reperfusion, surgery during hospital stay, recurrent AMI, postinfarction angina, hypoxaemia, heart failure, pericarditis Area of tissue damage measured by ECG mapping and cardiac enzymes (CK-MB)
Exclusions	People with complicated AMI, congestive heart failure, pulmonary disease, COPD or anaemia
Length of follow-up	10 days
Clinical Context and parallel care	Context of primary PCI
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Death	Low risk	This was an open-label trial (but absence of blinding unlikely to introduces bias in this outcome)
Blinding (performance bias and detection bias) Pain (or surrogate)	Unclear risk	Not applicable in this trial (pain was not a variable evaluated in the study)
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	This was an open-label trial (but the absence of blinding unlikely to introduce bias in this outcome)
Incomplete outcome data (attrition bias) Death	High risk	While mortality was adequately reported for included participants, there was inadequate description of exclusion postrandomisation in each group (e.g. failed revascularisation)

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Ukholkina 2005 *(Continued)*

Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	High risk	There was inadequate description of exclusion postrandomisation in each group
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Inadequate description of exclusion postrandomisation in each group (e.g. failed revascularisation). Consequently, these participants are not included in the infarct size comparison. There were problems of consistency in the measurement process of ECG mapping done to estimate infarct size
Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	Not applicable in this trial
Selective reporting (reporting bias)	High risk	We have no information about the protocol, but the infarct size estimation was only reported in 31 patients in the oxygen group and no information in the air group
Other bias	High risk	See baseline imbalances
Baseline characteristics	High risk	The groups were different at baseline in two important variables: 1. Clinical class Killip and Kimball (Killip II 10% O_2 versus 1% air group, P = 0.08) 2. Time to revascularisation 41 minutes shorter in the air group

Wilson 1997

Methods	Randomised, open-label, controlled trial
Participants	People with confirmed AMI presenting within 24 h of onset of symptoms Clinical setting: single-site coronary care unit in the UK N randomised = 50. N analysed = 42 (dropouts: 1 death, 1 stroke, 4 withdrew consent, 2 incomplete data collection) Mean age: oxygen 65 years, air 64 years Sex: 59% men
Interventions	Oxygen by face mask at 4 L/min versus normal air over 24 h
Outcomes	24 hours for Hypoxaemia, arrhythmias, cardiac enzymes.
Exclusions	People with heart failure, cyanosis central or pulmonary disease requiring O_2
Length of follow-up	Discharge
Clinical Context and parallel care	Thrombolysis period
Notes	The primary purpose of this trial was to look at the effect of oxygen on hypoxaemia.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Wilson 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Sealed envelopes for randomisation
Blinding (performance bias and detection bias) Death	Low risk	This was an open-label trial (but the absence of blinding is unlikely to introduce bias in this outcome)
Blinding (performance bias and detection bias) Pain (or surrogate)	High risk	This was an open-label trial, therefore the risk of bias in this outcome cannot be ruled out
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not relevant to this study
Incomplete outcome data (attrition bias) Death	High risk	8 out of 50 missing data (group not specified); 1 death, 1 stroke, 4 withdrew consent, 2 incomplete data
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	Unclear risk	Not relevant in this study
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not relevant in this study
Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	Not relevant in this study
Selective reporting (reporting bias)	High risk	The main variables of the study were incidence and degree of hypoxaemia and the effect of oxygen administration. The main outcome of this review (death) was not reported, and in fact the only participant who died was not included in the analysis
Other bias	Low risk	Other biases were not identified
Baseline characteristics	Low risk	Consecutive participants, similar age, smoking and diabetes

AMI: myocardial infarction; **AUC**: area under the curve; **BNP**: brain natriuretic peptide; **COPD**: chronic obstructive pulmonary disease; **ECG**: electrocardiogram; **MC**: medium concentration: **MRI**: magnetic resonance imaging; **PCI**: percutaneous coronary intervention; **PCA**:percutaneous coronary angioplaty. **SD**: standard deviation; **STEMI**: ST-segment elevation myocardial infarction.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AMIHOT 2003	Wrong intervention: aqueous oxygen therapy in STEMI
Dekleva 2004	Wrong intervention: hyperbaric oxygen versus air in participants after thrombolysis in AMI

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Study	Reason for exclusion
Dotsenko 2007	Wrong intervention: hyperbaric oxygen versus air in conventionally treated participants with AMI
Haude 2007	Wrong intervention: supersaturated oxygen therapy after percutaneous coronary intervention in AMI
Kerr 1975	Different intervention: nitrous oxide 50% with or without oxygen 50% versus air in participants with AMI
Shandling 1997	Wrong intervention: hyperbaric oxygen
Slagboom 2005	Wrong intervention: haemoglobin-based oxygen therapeutics in elective PCI

AMI: acute myocardial infarction; **PCI**: percutaneous coronary intervention; **PCA**: percuaneous coronary angioplasty; **STEMI**: ST-segment elevation myocardial infarction.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12609000466246

Trial name or title	A randomised controlled trial comparing controlled oxygen therapy versus high flow oxygen therapy for acute myocardial infarctions in the pre-hospital setting (no specific name available)
Methods	Randomised controlled trial, parallel design with open label and allocation concealment
Participants	People with chest pain and suspicion of acute coronary syndrome attended by Tasmanian ambulance service in the Launceston region
Interventions	High flow oxygen 8-15 L/min by non-breather mask compared to oxygen therapy to maintain oxygen saturation between 92%-96%
Outcomes	Primary outcome: mortality during ambulance or in the hospital stay Secondary outcomes: 1. Time to resolution of chest pain using a 0-10 scale and an electronic system for reporting data 2. Length of hospital stay
Starting date	Theoretically January 2012
Contact information	Dr Michael Austin, Menzies Research Institute (Private Bag 23) Hobart TAS 7001. maaustin@utas.edu.au
Notes	Not recruiting yet (register visited last time 30 June 2016)

NCT01423929

Trial name or title	Supplemental oxygen in catheterization coronary emergency reperfusion (SOCCER)
Methods	Multicentre single-blind randomised controlled trial, parallel design and allocation concealment
Participants	Normoxic STEMI ambulance patients with symptom duration less than 6 hours (bypassing the emergency department)

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NCT01423929 *(Continued)*

Interventions	Oxygen 10 L/min by oxymask versus room air
Outcomes	Primary outcomes: infarct size estimated by MRI at day 4, myocardial salvage index by MRI Secondary outcomes: TIMI flow during PCI, echocardiography (acute and 6 months after AMI), pro-BNP, and dose of opioids
Starting date	January 2012
Contact information	Mahin Akbarzadeh (Skåne University Hospital at Lund)
Notes	2 hospitals with PPCI capabilities. Verbal informed consent in ambulance and delayed written informed consent

NCT01787110

Trial name or title	An efficacy and outcome study of supplemental oxygen treatment in patients with suspected myocardial infarction (DETO2X-AMI)
Methods	Multicentre open label registry-based randomised clinical trial
Participants	Normoxic patients (saturation > 90%) in emergency medical service or emergency departments with suspicion of acute myocardial infarction (STEMI and non STEMI) within the last 6 h
Interventions	Oxygen 6 L/min by oxymask started as soon as possible and maintained for 13 h vs no oxygen except if saturation < 90% (repeatedly checked)
Outcomes	Primary outcome: 1 year all-cause mortality. Secondary outcomes: 30-days mortality, major cardiac coronary events (MACE) in 30 days and 1 year including reinfarction and hospitalisations for cardiac failure. In sub-studies, echocardiograpy and cardiac magnetic resonance will be used to assess infarct size and cardiac function.
Starting date	April 2013
Contact information	Leif Svensson and Robin Hofmann (Södersjukhuset. Stockholm, Sweden, 11883)
Notes	The protocol and feasibility studies have been published (see ongoing trials)

NCT02290080

Trial name or title	Determination of the role of oxygen in suspected acute myocardial infarction by biomarkers (DETO2X-bio)
Methods	Single blind (outcomes assessor) randomised clinical trial
Participants	Normoxic patients (saturation > 90%) in emergency medical service or emergency departments with suspicion of acute myocardial infarction (STEMI and non STEMI) within the last 6 h
Interventions	Oxygen 6 L/min by oxymask started as soon as possible and maintained for 13 h vs no oxygen except if saturation < 90% (repeatedly checked)

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NCT02290080 *(Continued)*

Outcomes	Plasma concentration levels over time of biomarkers of oxidative stress, apoptosis, inflammation and platelet aggregation
Starting date	October 2014 (estimated study completion October 2015)
Contact information	Leif Svensson & Robin Hofmann (Södersjukhuset. Stockholm, Sweden, 11883
Notes	This study is a substudy of DETO2X-AMI

AMI: acute myocardial infarction; **BNP**: brain natriuretic peptide; **MRI**: magnetic resonance imaging; **PCI**: percutaneous coronary intervention; **TIMI**: thrombolysis in myocardial infarction.

WHAT'S NEW

Date	Event	Description
12 October 2016	New citation required but conclusions have not changed	The addition of one new trial changed the results of this review but not the conclusions. This version includes a 'Summary of findings' table with GRADE assessment, unlike the previous version.
3 August 2015	New search has been performed	We conducted a new search in June 2016 and identified one new trial for inclusion along with four ongoing trials.

HISTORY

Protocol first published: Issue 2, 2008
Review first published: Issue 6, 2010

Date	Event	Description
7 April 2013	New citation required but conclusions have not changed	One new study included
7 April 2013	New search has been performed	The updated search was conducted in May 2013, and identified one new trial for inclusion and three ongoing trials.

CONTRIBUTIONS OF AUTHORS

Juan Cabello provided expert advice, co-wrote the protocol and helped with quality assessment, contacted authors for further information, data extraction, analysis, writing the discussion and entering data into RevMan.

Amanda Burls co-wrote the protocol, contacted authors for further information and contributed to quality assessment, data extraction, analysis, writing the discussion, and entering data into RevMan.

Sue Bayliss undertook the electronic searches, helped obtain papers and proofread the review.

Jose Emparanza Knorr co-wrote the protocol and contributed to quality assessment, data extraction, analysis and writing of the discussion.

Tom Quinn provided expert advice, contacted experts to find unpublished studies and contributed to quality assessment, data extraction, revision of the draft paper and writing of the discussion.

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DECLARATIONS OF INTEREST

None on starting this review. After starting this systematic review two of the authors (AB and TQ) have put together, with other clinical colleagues, a proposal for a randomised controlled trial in the UK of oxygen for AMI in the pre-hospital setting. This proposal was not supported, and therefore the protocol was cancelled.

Tom Quinn was a member of the steering group for the STREAM Trial (Boehringer Ingelheim) and the EUROMAX trial (Medicines Company), and he was a local collaborator/principal investigator for the ATLANTIC trial (Astra Zeneca). All of these were studies of pre-hospital management of patients with acute coronary syndrome.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- None, Not specified.

No financial support was received for this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Data were too sparse to permit adequate analysis of the subgroups that had been prespecified for exploration.

We made three changes:

1. One minor change in the search strategy to improve the sensitivity, i.e. the inclusion of the text word 'oxygenotherapy' in the title (the original search failed to pick up the Russian article and we looked to see if it was in MEDLINE and, if so, why the search strategy had missed it);
2. After the protocol was published, a new version of the *Cochrane Handbook for Systematic Reviews of Interventions* recommended a new approach to assessment of risk of bias, so we changed our method of assessment to be consistent with the recommendations (Higgins 2011).
3. In this version of the review, we have used the nine-point scale suggested by GRADE to classify the clinical importance of the outcomes (Guyatt 2008).
4. In this version, we include the 'Summary of findings' table with GRADE assessment, unlike the previous version.

INDEX TERMS

Medical Subject Headings (MeSH)

*Oxygen Inhalation Therapy [adverse effects] [mortality]; Air; Analgesics [therapeutic use]; Cause of Death; Intention to Treat Analysis; Myocardial Infarction [mortality] [pathology] [*therapy]; Pain Measurement [methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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